通过尿蛋白质组探究抑郁症和双相情感障碍的差异

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摘要：如何鉴别诊断抑郁症与双相情感障碍一直都是临床急需解决的重要问题。本研究从尿液蛋白质组学的角度出发，从两家医院收取年龄相近的尿液样本，利用成组分析和一对多分析两种方法，探究鉴别诊断抑郁症与双相情感障碍的候选生物标志物。成组分析的实验结果显示，抑郁组与双相组相比，在严格的筛选条件下，筛选标准为FC≥2 或≤0.5，双尾非配对 t 检验 $P < 0.01$ 可鉴定到 108 个差异蛋白，随机产生的差异蛋白平均为 3.7 个，这些蛋白和疾病差异相关的可信度 96.6 %。在一对多分析中，有 24 个差异蛋白被 13 例抑郁患者样本共同鉴定到，其中的 16 个差异蛋白在所研究的所有抑郁患者中呈现出完全一致的表达变化趋势，且其中有 6 个差异蛋白与免疫球蛋白有关；有 41 个差异蛋白被 13 例中的 12 例抑郁患者样本共同鉴定到，且其中的 19 个差异蛋白在 12 例抑郁患者中呈现出完全一致的表达变化趋势，这些结果均反映出两组患者之间的差异蛋白具有很强的一致性。12 例及以上抑郁患者样本共同鉴定到的差异蛋白富集到了多个与免疫系统相关的生物学过程和信号通路，这一结果和以往的研究一致：免疫机制可能是重度抑郁症的发病机制之一，而具有主要免疫靶点的药物可以改善抑郁症状。未来或许可通过观测抑郁症患者机体的免疫状态对精准治疗抑郁症提供方向和依据。本文研究结果显示尿液蛋白质组可以鉴别诊断抑郁症与双相情感障碍，为治疗抑郁症与双相情感障碍提出可能的机制和潜在的靶点，为今后疾病的鉴别诊断及精准治疗提供了工具。

关键词：尿液，蛋白质组学，抑郁症，双相情感障碍

Exploring differences between depression and bipolar disorder through the urinary proteome

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Abstract: How to differentiate the diagnosis of depression and bipolar disorder has always been an important problem that needs to be solved urgently in clinical practice. In this study, from the perspective of urine proteomics, urine samples of similar age were collected from two hospitals to investigate the candidate biomarkers for differentiating the diagnosis of depression and bipolar disorder using both group analysis and one-to-many analysis. The experimental results of the paired group analysis showed that 108 differential proteins were identified in the depressed group compared to the bipolar group under strict screening conditions with screening criteria of $FC \geq 2$ or ≤ 0.5 and a two-tailed unpaired t-test of $P < 0.01$, with an average of 3.7 randomly generated differential proteins, and a confidence level of 96.6 % for the correlation between these proteins and the disease difference. In the one-to-many analysis, 24 differential proteins were co-identified by the samples of 13 depressed patients, 16 of which showed a completely consistent trend of expression changes in all depressed patients studied, and 6 of which were associated with immunoglobulins; 41 differential proteins were co-identified by the samples of 12 depressed patients out of 13, and 19 of which showed a completely consistent trend of expression change in the These results reflect the strong consistency of differential proteins between the two groups of patients. 12 or more samples from depressed patients were enriched for differential proteins related to multiple biological processes and signaling pathways associated with the immune system, which is consistent with previous studies: immune mechanisms may be one of the pathogenetic mechanisms of major depression and that drugs with major immune targets can improve depressive symptoms. In the future, it may be possible to observe the immune status of patients with depression to provide direction and basis for the precise treatment of depression. The results of this paper show that urine proteomics can differentiate between depression and bipolar disorder, suggest possible mechanisms and potential targets for the treatment of depression and bipolar disorder, and provide a tool for future differential diagnosis and precision treatment of the diseases.

Keywords: urine, proteomics, depression, bipolar disorder

1. 前言

1.1 尿液生物标志物

生物标志物是能够从客观的角度去反映正常的病理过程以及生理过程的指示物[1]，在临床上，生物标志物能够在不同的阶段预测、监测和诊断多因素的疾病[2]。相较于目前应用更广泛的血液生物标志物，尿液生物标志物的潜能尚未开发完全。尤其是在疾病的早期诊断和状态预测方面。由于血液中存在内环境稳态机制的调节，由疾病导致的血液蛋白质组变化被代谢排出，不能在疾病早期显现明显的变化。而尿液是由肾小球过滤血浆产生的，不受稳态机制的调节，变化灵敏，疾病在早期的微小变化都能够在尿液中观察到。且根据研究结果显示，观察到的变化远比血液早，比病理切片要早，甚至比疾病症状的显现还要早，可以应用于疾病的早期诊断。例如，(1)本研究组的张繁霜等[3]研究发现，在阿尔兹海默症的转基因小鼠的脑部淀粉斑块沉积出现之前，尿中就有 29 个蛋白发生变化，而其中有 24 个蛋白被报道过与阿尔兹海默症相关或作为标志物；(2)本研究组的吴建强等[4]在 Walker256 皮下瘤大鼠模型中，在皮下瘤被触及之前尿液中有 10 个蛋白发生变化；(3)本研究组的 Zhang Y 等[5]在慢性胰腺炎大鼠模型中，在第 2 周病理尚未出现变化前，尿液中鉴定到 15 个差异蛋白，其中有 5 个被报道过与胰腺炎有关；(4)本研究组的倪艳颖等[6]在脑部注射 C6 细胞胶质瘤大鼠模型中，在影像学出现症状之前尿蛋白发生变化；(5)本研究组的张繁霜等[7]在硫代乙酰胺诱导

的肝纤维化大鼠模型中，在病理变化之前，尿液中鉴定到 40 个差异蛋白，有 15 个被报导过与纤维化相关；(6)本研究组的 Yin 等[8]发现，肥胖 2 型糖尿病大鼠血糖升高之前，尿糖水平已经呈现频繁紊乱状态，具有指示早期糖尿病的意义；(7)本研究组的黄鹤等人[9]将大鼠暴露于传统香烟的烟雾中，仅在暴露两周时就筛选到了已被报道过的慢性阻塞性肺疾病(COPD)的生物标志物。经过对比研究发现，当肿瘤细胞在皮下[4]、肝脏[7]、骨[10]、肺[11]和脑部[6]不同的器官生长时，尿蛋白的变化不同，这表明尿液具有区分相同肿瘤细胞在不同器官生长的潜能。且在样本获取方面，尿液的获取更加无创、易得[12]，可见尿液是良好的生物标志物来源。

目前尿液中的生物标志物的检测越来越受到检验医师和研究者的关注，且已经被运用到多种疾病的治疗和研究中，用于探索疾病机制、药物靶点及基因功能等。本研究组的吴建强等[13]检测博来霉素诱导的肺纤维化大鼠模型尿液蛋白质组，发现胰岛素样生长因子 1(insulin-likegrowth factors-1, IGF-1)通路等重要生物学通路发生变化。在此之前，Choi 等[14]发现，用抗体阻断 IGF-1 通路会显著延长博来霉素诱导的肺纤维化动物模型的寿命。这显示了尿液蛋白质组研究用于探索疾病机制和寻找药物靶点的巨大潜力。本研究组的鲍艺今等[15]建立急性低氧大鼠模型，尿液蛋白质组变化显示谷胱甘肽的代谢和缺氧应激反应密切相关，为高原反应的预防和治疗提供了线索。本研究组的孟文书等[16]发现，易卒中高血压大鼠尿液蛋白质富集到的生物学通路与降压药物的分子机制有关，例如醛固酮和肾素-血管紧张素等的信号通路，显示出尿液蛋白质组学对于探索疾病药物靶点的应用前景。鉴定转基因动物模型尿液蛋白质组也可以作为研究基因功能的手段。本研究组的华元瑞等[17]检测无表型的基因编辑动物的尿蛋白质组，从蛋白质水平推测基因功能。

在药理学、毒理学方面，尿液生物标志物可以灵敏的反映出药物对机体的影响，可以用于临床预测药物疗效、检测药物毒副作用，为及时调整治疗措施提供参考和依据。Davies JC 等[18]预测成年系统性红斑狼疮（SLE）患者对利妥昔单抗治疗的疗效、沙库巴曲缬沙坦比缬沙坦治疗慢性心力衰竭的效果更显著。本研究组的魏静等[19]在尿液中发现的标志物组可用于判断他汀类药物相关肌肉损伤症状程度。本研究组的鲍艺今等[20]发现，大鼠服用复方丹参滴丸后尿液中变化显著的蛋白质与糖酵解、脂类代谢等生物学通路密切相关，这显示出该中药对机体产生的整体影响并一定程度反映其治疗心血管疾病的作用机制，为中药作用机制和疗效的研究提供了新方法。本研究组的赵晨阳等[21]比较分析了分别服用不同厂家生产、同一剂型的阿托伐他汀药物的大鼠尿液蛋白质组，为药物一致性评价提供了创新性的方法和思路。类似的研究还有硫代乙酰胺诱导得到的肝纤维化模型[7]、博来霉素诱导的肺纤维化模型[12]、二乙基二硫代氨基甲酸盐诱导的慢性胰腺炎模型[22]、阿霉素诱导得到的肾疾病模型[23]、香烟烟雾诱导的慢性阻塞性肺病模型的尿液蛋白质组[9]，这些疾病动物模型同时也是毒理模型。由于尿液可以灵敏地反映出药物对机体的影响，动物模型尿液蛋白质组的监测是药理学和毒理学研究的良好途径[24]。

尿液生物标志物不仅应用于实验动物模型中，更广泛应用于临床样本，对疾病的预测、早期诊断和疾病分型等有着良好的指示作用。在呼吸系统疾病中，尿液蛋白质组可以为疾病的诊断和预后提供参考。Young BL 等人[25]发现，尿蛋白质组可以鉴定特征明确的活动性肺结核(TB)与非 TB 患者尿液中结核病特异性生物标志物。Denise Traxler 等人[26]对 253 名因急性加重而住院的 COPD 患者进行尿蛋白质组检测，发现尿液中 HSP27 含量在急性加重期降低，可能为第一年内因急性加重而住院的 COPD 患者的管理提供有价值的信息。2019 年以来，新型冠状病毒(CoVID-19)肺炎的流行是对全球人口健康的威胁。研究者陆续发现，CoVID-19 患者尿液蛋白质组显示出相关的病理生理状态变化[27]，可用于探究新冠肺炎的发病机制，且早期感染患者体内存在显著的免疫抑制[28]；研究发现，尿液中检测到的细胞因子及其受体多于血清[29]，分析患者体内特异的信号通路可寻找潜在的治疗靶点[30]。在肾脏

疾病中，尿液蛋白质组可以为疾病的发病机制提供思路。2020 年 Hao 等人[31]在慢性肾病(CDK)患者的尿液样本中成功鉴定出 42 个低丰度蛋白和 46 个高丰度蛋白。从这些调控蛋白中鉴定出 7 条与 CKD 及其并发症相关的 KEGG 通路，为 CDK 的发病机制及其并发症提供新的生物标志物。尿液蛋白质组在良性恶性肿瘤的鉴别上同样发挥着很好的作用。2021 年 Ni 等人[32]对卵巢癌的良恶性肿瘤患者进行尿蛋白质组学分析，并将其中的 5 种蛋白作为良恶肿瘤分类器。结果表明尿液蛋白质组的新型分类器为卵巢良恶性肿瘤提供了一种很有前途的无创诊断生物标志物。

近年来，有许多研究表明，尿液蛋白质组学还可以在神经退行性疾病中观测到生物标志物。Mann 研究团队将蛋白质组学技术、遗传筛查与机器学习相结合，尿液蛋白质组可以将携带不同帕金森病相关突变基因、不同疾病表现的人区分开，为发现帕金森病生物标志物和为患者分层提供了一个有价值的策略[33]。Yumi Watanabe 等人[34]在尿液蛋白质组中发现了阿尔兹海默症(AD)的潜在标志物 ApoC3。尿液蛋白质组同样可以为精神疾病的早期诊断和个体化治疗提供线索。本研究组的孟文书等[35]发现，筛选出的尿蛋白质生物标志物组可以有效区分不同年龄组的健康儿童和自闭症儿童，有潜力辅助自闭症的早期诊断和干预，并且运用随机分组方法验证结果的可信度。Wang 等[36]发现，自闭症患者蛋白质组显示出与疾病机制有关的生物学通路变化。本研究组的郇宇航等[37]检测了对于抗抑郁药物有不同反应的重度抑郁症患者的差异表达蛋白质，发现尿液生物标志物有潜力预测重度抑郁症患者的有效治疗措施，可为精准化治疗提供线索和依据，提高患者的生活质量。

1.2 抑郁症与双相情感障碍

抑郁症(Depression)是一种情绪障碍，患者的特征是具有持续的悲伤感以及体验不到快乐，并伴有日常功能障碍。在全球范围内，抑郁症是导致残疾和生产性寿命损失的主要原因[38]。在美国，抑郁症的发病率为 5%-10%，但在某些初级保健或专科医疗机构，发病率可高达 40%-50%[39]。尽管存在高质量的循证疗法，但只有约一半的抑郁症患者得到了适当的治疗[40]。抑郁症对糖尿病等许多常见的普通并发症的发病率、费用和治疗效果都有重大影响[41]，同时也是自杀的主要风险因素，1999 至 2018 年间，美国的自杀率上升了约 35%[42]。抑郁症的病理生理原因尚不清楚，目前没有临床上有用的生物诊断标记或生物筛查试验[43]。

双相情感障碍(Bipolar Disorder, BD)，又称躁郁症，是一种慢性疾病，伴有严重的衰弱症状，会对患者及其照顾者产生深远的影响[44]。双相情感障碍通常始于青春期或成年早期，会对患者的身心健康、教育和职业功能以及人际关系产生终生的不良影响[45]。尽管 BD 不像重度抑郁障碍（Major Depressive Disorder, MDD）那样常见，但在美国，BD 的终生患病率很高（估计约为 4%），不同种族、族裔和性别的患病率相似[46][47]，长期结果一直不理想[48]。由于 BD 的躁狂或抑郁症状往往很严重，而且在患者的一生中会反复出现，因此这种疾病会给患者、护理人员和社会带来巨大的负担。BD 患者的发作会反复切换以躁狂或抑郁症状为特征的病理性情绪状态，其间夹杂着相对正常的情绪期[49]。躁狂和抑郁症状的正式定义包含在最近更新的《精神疾病诊断与统计手册第五版》（DSM-5）[50]中。值得注意的是，在 DSM-5 中，BD 的抑郁发作与 MDD 的定义标准相同，因此区分 BD 与 MDD 通常取决于是否有躁狂或躁狂症状史[51]。

由于 BD 早期通常表现为抑郁症状，若此时诊断为抑郁症并用药，可能会加重患者病情。如果临床医生意识到患者可能患有 BD，就能增加成功识别和适当治疗的可能性，从而对短期疗效和长期病程产生有利影响[48][51][52]。目前用于双相情感障碍筛查工具主要有问卷测试和确诊性临床访谈两种，情绪障碍问卷(Mood Disorder Questionnaire, MDQ)和国际综合诊断访谈 3.0 版(Composite International Diagnostic Interview, version 3.0, CIDI 3.0)是常用的筛查工具，其得分超过特定的临界值就会引起对躁狂症的怀疑[53][54]。但是尚未有客观的生理性指标用于鉴别诊断双相情感障碍，因此本文收取健康人、抑郁症患者和双相情感障碍患者的尿

液样本，以尿液蛋白质组学为基础，探究能否在尿液中找到鉴别诊断抑郁症与双相情感障碍的生物标志物（如图 1）。

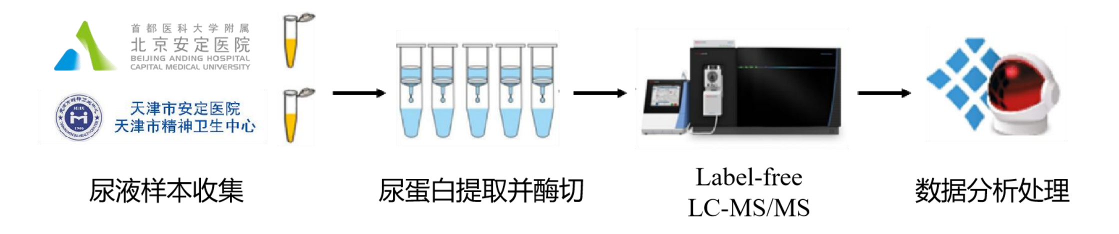


图 1 通过尿蛋白质组探究抑郁症和双相情感障碍的差异的技术路线

2. 材料与方法

2.1 参与者尿液样本收集

本研究获得了首都医科大学附属北京安定医院人体研究和伦理委员会的批准[(2022)科研第(14)号-202221FS-2]，获得了天津安定医院伦理委员会的批准（2019-18）。所有参与者均提供了书面知情同意书。参与者来自首都医科大学附属北京安定医院和天津市安定医院，样本采集时间为 2022 年 12 月至 2023 年 4 月。排除精神分裂症、其他精神病性障碍者、人格障碍或精神发育迟滞诊断者的病例，并选取了年龄在 18-23 之间的未用药样本。参与者样本包含 11 例健康人样本，11 例双相情感障碍患者样本以及 13 例抑郁症患者样本。收集的尿液样本都放入-80℃冰箱保存。

表 1 收集的样本信息与统计结果

样本信息		健康（n=11）	双相（n=11）	抑郁（n=13）
性别	男	6	6	8
	女	5	5	5
年龄	平均值	21.1±2	20.0±2	20.7±2
	年龄范围	20-23	18-22	19-22

2.2 尿液样品的处理

尿蛋白提取和定量：将收集到的尿液样本在 4℃的条件下 12000×g 离心 30 min，将上清液转移到 50 mL 离心管中。后加入二硫苏糖醇溶液（Dithiothreitol, DTT, Sigma）至终浓度为 20 mM，震荡混匀后，水浴 37℃加热 1 h，冷却至室温。加入碘乙酰胺（Iodoacetamide, IAA, Sigma）至终浓度为 50 mM，混匀后室温避光反应 40 min。加入六倍体积的预冷无水乙醇，均匀混合后在-20℃条件下沉淀 24 h。第二天将混合液于 4℃，12000×g 离心 30 min，弃上清。将蛋白沉淀重悬于裂解液中(含 8 mol/L 尿素，2 mol/L 硫脲，25 mmol/L 二硫苏糖醇，50 mmol/L Tris)。于 4℃条件下 12000×g 离心 30 min，取上清置于新的 EP 管内。用 Bradford 法测量蛋白质浓度。

尿蛋白酶切：取 100 μg 尿蛋白样品加入到 10 kDa 超滤管的滤膜(Pall, Port Washington, NY, USA)上，置于 EP 管中，加入 25 mmol/L NH_4HCO_3 溶液使总体积为 200 μL。而后进行洗膜操作：①加入 200 μL UA 溶液(8 mol/L 尿素，0.1 mol/L Tris-HCl，pH 8.5)，按照 14000×g 5 min 18℃的条件离心洗涤 2 次；②上样：加入刚刚处理的样品，在 14000×g 40 min 18℃条件下进行离心；③加入 200 μL UA 溶液，18℃条件下按 14000×g 离心 40 min，重复 2 次；④加入 25 mmol/L NH4HCO3 溶液，在 14000×g 40 min 18℃条件下离心，重复 3-4 次；⑤按照胰酶：蛋白为 1：50 的比例加入胰蛋白酶（Trypsin Gold, Promega, Fitchburg, WI, USA）进

行消化，37℃水浴 12-16 h。第二天 13000×g 30 min 4℃条件下离心收集肽段，通过 HLB 柱(Waters，Milford，MA)除盐，使用真空干燥仪抽干，在-80℃条件下保存。

2.3 LC-MS/MS 串联质谱分析

将酶解后的样品溶解于 0.1%的甲酸中，使用 BCA 试剂盒对肽段进行定量，将肽段浓度稀释为 0.5 μg/μL。取每个样品 4 μL 制备混合多肽样，按照说明书，使用高 pH 反相肽分离试剂盒(Thermo Fisher Scientific)进行分离。离心收集十份流出液（Fractions），使用真空干燥仪抽干后用 0.1%甲酸复溶。以样品 ：iRT 为 10 : 1 的体积比例加入 iRT 试剂(Biognosys, Switzerland)，以校准提取的肽峰的保留时间。为了进行分析，每个样品取 1 μg 肽段，使用 EASY-nLC1200 色谱系统(Thermo Fisher Scientific, USA)和 Orbitrap Fusion Lumos Tribrid 质谱仪(Thermo Fisher Scientific, USA)进行质谱分析并采集数据。

为了生成谱库，将分离得到的 10 个 Fractions 在 Data Dependent Acquisition(DDA)模式下进行了质谱分析。质谱数据采用高灵敏度模式采集。在 350-1500m/z 范围内获得了一个完整的质谱扫描，分辨率设置为 60,000。单个样品采用 Data Independent Acquisition(DIA)模式进行分析。采用具有 36 个窗口的 DIA 方法进行 DIA 采集。每 8 个样品后，对汇集肽进行单次 DIA 分析作为质量控制。

2.4 数据库搜索和 Label-free DIA 定量

将从液相-质谱联用采集到的原始数据（RAW 文件），导入 Proteome Discoverer（version 2.1, Thermo Scientific），使用 SwissProt 数据库（分类法：Homo；包含 20346 个序列）。进行比对，并将 iRT 序列添加到数据库中。然后将搜索结果导入 Spectronaut Pulsar(Biognosys AG, Switzerland)，进行处理和分析。通过将 MS2 中各自片段离子的峰面积相加，计算出肽的丰度。蛋白质强度由各自的肽丰度相加计算蛋白质丰度。

2.5 数据分析

每个样品均进行了 3 次技术重复，取平均值用于统计学分析。将鉴定到的蛋白进行比较，筛选差异蛋白。差异蛋白宽松筛选条件为：组间变化倍数（FC, Fold change）≥1.5 或≤0. 67，双尾非配对 *t* 检验分析的 *P* 值＜0.05。差异蛋白严格筛选条件为：组间变化倍数（FC, Fold change）≥2 或≤0. 5，双尾非配对 *t* 检验分析的 *P* 值＜0.01。对筛选到的差异蛋白使用悟空平台（https://www.omicsolution.org/wkomic/main/）、Uniprot 网站（https://www.uniprot.org/）和 DAVID 数据库（https://david.ncifcrf.gov/）进行功能富集分析。并在 Pubmed 数据库（https://pubmed.ncbi.nlm.nih.gov）中检索已报道文献，从而对差异蛋白进行功能分析。

3. 结果与讨论

3.1 成组比较尿液蛋白质组的变化分析

3.1.1 尿液蛋白质组的鉴定及功能分析

将 11 例健康人样本，11 例双相情感障碍患者样本以及 13 例抑郁症患者样本的尿液样品酶切产生的肽段进行 LC-MS/MS 串联质谱分析。总共鉴定到 2612 个蛋白（特异性多肽≥2 个，蛋白水平 FDR<1%）。

3.1.1.1 健康组与双相组对比尿液蛋白质组的鉴定及功能分析

将 11 例健康人组样本与 11 例双相情感障碍患者组样本进行比较。宽松条件下，筛选差异蛋白的标准为：$FC \geq 1.5$ 或 ≤ 0.67，双尾非配对 t 检验 $P < 0.05$，可以鉴定到 67 个差异蛋白（表 S1）。严格条件下，筛选标准为 $FC \geq 2$ 或 ≤ 0.5，双尾非配对 t 检验 $P < 0.01$，可以鉴定到 7 个差异蛋白（表 2）。此前，Cannon 等人[55]发现，在未服药的双相情感障碍患者中，丘脑、纹状体、岛叶和扣带回皮质中的脑血清素转运体(brain serotonin transporter)水平升高，而 2011 年 X Liu 等人[56]在此基础上开展全基因组关联研究，认为半乳糖突变酶(Galactose mutarotase, GALM)的非同义多态性与人类丘脑中血清素转运体的结合潜力有关。

而本文的结果为 X Liu 等人[56]的结论提供了强有力的佐证依据。

表 2 健康人与双相患者相比的差异蛋白 (FC≥2 或≤0.5, P<0.01)

Accession	Protein names	trend	FC	P
Q96C23	Galactose mutarotase	↓	0.43	7.19E-04
C9IZ46	Protein shisa-5	↓	0.43	1.67E-03
O43852	Calumenin	↓	0.47	4.54E-03
P10451	Osteopontin	↑	2.00	7.75E-03
O60293	Zinc finger C3H1 domain-containing protein	↑	2.36	8.18E-04
O95433	Activator of 90 kDa heat shock protein ATPase homolog 1	↑	2.40	8.47E-06
P08473	Neprilysin	↑	2.55	1.33E-03

将宽松条件下健康组与双相组鉴定到的差异蛋白进行功能分析，共富集到内肽酶活性负调节(negative regulation of endopeptidase activity)、蛋白水解(proteolysis)、细胞粘附(cell adhesion)等 26 个生物学过程和肾素-血管紧张素系统(Renin Angiotensin System，RAS)、补体和凝血级联反应(Complement and coagulation cascades)、蛋白质消化和吸收(Protein digestion and absorption)3 个信号通路（表 S2）。其中，Xu You 等人[57]根据筛选到的潜在 BD 诊断生物标记物，同样富集到了蛋白水解等生物学过程，与本文研究结果一致。2022 年 Meng-Yuan Shang 等人在探究智商高低与 BD 潜在风险的相关性实验中，同样富集到了细胞粘附和钙离子结合等生物学过程。Barbosa IG[58]等人对 RAS 与 BD 的关系进行了系统性的综述，尽管 Barbosa IG 等人仍未能得出二者关系的确切结论，但总结了多篇支持 RAS 在中枢神经系统和神经精神疾病中发挥作用的研究[59-61]，并提出需要对 BD 患者的 RAS 进行评估的建议。

3.1.1.2 健康组与抑郁组对比尿液蛋白质组的鉴定及功能分析

将 11 例健康人组样本与 13 例抑郁症患者组样本进行比较。宽松条件下，筛选差异蛋白的标准为：FC ≥ 1.5 或 ≤ 0.67，双尾非配对 t 检验 $P < 0.05$，可以鉴定到 276 个差异蛋白（表 S3）。严格条件下，筛选标准为 FC ≥ 2 或 ≤ 0.5，双尾非配对 t 检验 $P < 0.01$，可以鉴定到 61 个差异蛋白（表 3）。有研究表明，叶酸主要由神经组织代谢，5-甲基四氢叶酸(5-MTHF)是血液和脑脊液中叶酸的主要循环形式，而叶酸受体α（Folate receptor alpha, FR-α）是介导叶酸通过生物膜的转运的主要途径之一，在上皮细胞中普遍表达，对 5-MTHF 具有极高的亲和力，能在叶酸水平较低时将 5-MTHF 从血液中转运到上皮细胞中[62][63]。2022 年 Nelson Siu Kei Lam 等人[64]将叶酸(folate)及其衍生物在治疗精神疾病中的潜在用途进行了系统性综述，得出结论为口服左旋叶酸或 5-甲基叶酸与改善重度抑郁症的临床疗效有关。除此之外，Carazo-Arias E 等人[65]2022 年针对氟西汀治疗抑郁症的反应性进行了研究，结果表明慢性氟西汀治疗会上调小鼠齿状回中原脑啡肽(Proenkephalin)的表达，且这种上调与治疗反应性有关。编码的 Mda-9/syntenin 的 SDCBP 基因能够激活 NF-κB 通路[66]，而 NF-κB 通路与抑郁症的发生和发展密切相关[67][68][69]，因此 Jiang W 等人[70]认为类风湿性关节炎患者重度抑郁症发生过程中，SDCBP 的变化可能通过复杂的分子调控网络控制抑郁症的发生，并可作为类风湿性关节炎伴重度抑郁症的潜在诊断指标，这与本文在健康人与抑郁症患者相比筛选到 syntenin-2 这一差异蛋白的结果互相印证。

将宽松条件下健康组与抑郁组鉴定到的差异蛋白进行功能分析，共富集到细胞粘附(cell adhesion)、纤溶负调节(negative regulation of fibrinolysis)、补体激活经典途径(complement activation, classical pathway)等 116 个生物学过程和细胞粘附分子(cell adhesion molecules, CAM)、溶酶体(lysosome)等 30 个信号通路（表 S4）。值得一提的是，健康组与 BD 组相比筛选到的差异蛋白同样富集到了细胞黏附这一生物学过程。同时 John Jayakumar JAK 等人[71]

研究发现 5-羟色胺通过与细胞相关的粘附作用在精神疾病以及神经精神类药物的积极和消极作用中所扮演的角色具有重要意义，包括抑郁症、双相情感障碍、精神分裂等。

表 3 健康人与抑郁患者相比的差异蛋白 (FC≥2 或≤0.5, P<0.01)

Accession	Protein names	trend	FC	P
P15328	Folate receptor alpha	↓	0.44	4.95E-05
O95445	Apolipoprotein M	↑	2.03	4.56E-03
P01210	Proenkephalin-A	↑	2.07	7.08E-03
Q13113	PDZK1-interacting protein 1	↑	2.10	6.97E-03
P50591	Tumor necrosis factor ligand superfamily member 10	↑	2.10	9.61E-03
O43493	Trans-Golgi network integral membrane protein 2	↑	2.10	2.28E-03
P14151	L-selectin	↑	2.12	4.79E-03
Q9HB75	p53-induced death domain-containing protein 1	↑	2.15	7.11E-03
P30047	GTP cyclohydrolase 1 feedback regulatory protein	↑	2.19	7.16E-03
P31025	Lipocalin-1	↑	2.22	9.26E-03
P04196	Histidine-rich glycoprotein	↑	2.27	6.06E-03
A0A087WYX9	Collagen type V alpha 2 chain	↑	2.37	1.38E-03
Q68CJ9	Cyclic AMP-responsive element-binding protein 3-like protein 3	↑	2.38	3.32E-03
Q86TY3	Armadillo-like helical domain-containing protein 4	↑	2.39	8.94E-03
A0A087WZW1	Colipase	↑	2.54	6.76E-03
A0A0J9YX35	Immunoglobulin heavy variable 3-64D	↑	2.55	4.92E-03
P01178	Oxytocin-neurophysin 1	↑	2.66	8.71E-04
O94919	Endonuclease domain-containing 1 protein	↑	2.68	5.88E-04
Q14118	Dystroglycan 1	↑	2.71	3.33E-03
P02765	Alpha-2-HS-glycoprotein	↑	2.75	3.22E-03
Q86UD1	Out at first protein homolog	↑	2.79	7.73E-03
Q92626	Peroxidasin homolog	↑	2.82	9.41E-03
F5H0U5	Glycolipid transfer protein	↑	2.86	8.92E-03
P16989	Y-box-binding protein 3	↑	2.87	4.64E-03
P11766	Alcohol dehydrogenase class-3	↑	2.88	1.87E-04
P12318	Low affinity immunoglobulin gamma Fc region receptor II-a	↑	2.89	9.59E-03
A0A0G2JSC0	Immunoglobulin lambda variable 5-45	↑	2.94	3.71E-03
P29692	Elongation factor 1-delta	↑	2.96	7.19E-04
P54826	Growth arrest-specific protein 1	↑	2.97	5.66E-03
Q92496	Complement factor H-related protein 4	↑	3.01	6.77E-04
P17655	Calpain-2 catalytic subunit	↑	3.12	1.77E-03
Q7Z794	Keratin, type II cytoskeletal 1b	↑	3.15	5.08E-03
P22304	Iduronate 2-sulfatase	↑	3.17	6.17E-03
P30044	Peroxiredoxin-5, mitochondrial	↑	3.20	4.60E-03
P68371	Tubulin beta-4B chain	↑	3.39	2.01E-03
A0A0C4DH72	Immunoglobulin kappa variable 1-6	↑	3.41	2.75E-03
P30475	HLA class I histocompatibility antigen, B alpha chain	↑	3.60	2.66E-03
P12931	Proto-oncogene tyrosine-protein kinase Src	↑	3.62	2.29E-04
Q92484	Acid sphingomyelinase-like phosphodiesterase 3a	↑	3.74	7.03E-03
Q96A22	Uncharacterized protein C11orf52	↑	4.27	4.93E-03

E9PL83	Pro-adrenomedullin	↑	4.39	6.36E-03
F5H1S8	Malectin	↑	4.67	1.41E-03
Q15833	Syntaxin-binding protein 2	↑	4.73	3.36E-03
P04279	Semenogelin-1	↑	4.86	1.63E-03
E7EMR3	Adhesion G protein-coupled receptor L3	↑	4.87	6.15E-04
Q9UHI8	A disintegrin and metalloproteinase with thrombospondin motifs 1	↑	4.89	4.37E-03
K7ELM9	Apolipoprotein C1	↑	5.05	2.39E-04
E9PGC5	protein-tyrosine-phosphatase	↑	5.29	9.03E-03
H7BY57	Neurofascin	↑	5.49	1.68E-03
P25786	Proteasome subunit alpha type-1	↑	5.71	1.14E-03
Q8WU39	Marginal zone B- and B1-cell-specific protein	↑	5.89	7.74E-03
A0A0A0MQV3	Kin of IRRE-like protein 2	↑	6.97	3.57E-03
O00401	Actin nucleation-promoting factor WASL	↑	7.12	3.17E-04
O60449	Lymphocyte antigen 75	↑	7.20	3.83E-03
Q86SF2	N-acetylgalactosaminyltransferase 7	↑	7.35	4.67E-03
Q8IZJ3	C3 and PZP-like alpha-2-macroglobulin domain-containing protein 8	↑	7.43	8.86E-03
O00144	Frizzled-9	↑	8.31	2.02E-03
P00742	Coagulation factor X	↑	10.39	4.09E-03
O95817	BAG family molecular chaperone regulator 3	↑	11.68	4.72E-03
A5D8V6	Vacuolar protein sorting-associated protein 37C	↑	13.18	7.35E-03
Q9H190	Syntenin-2	↑	21.77	9.21E-03

3.1.1.3 双相组与抑郁组对比尿液蛋白质组的鉴定及功能分析

将 11 例双相情感障碍患者组样本与 13 例抑郁症患者组样本进行比较。宽松条件下，筛选差异蛋白的标准为：$FC \geq 1.5$ 或 ≤ 0.67，双尾非配对 t 检验 $P < 0.05$，可以鉴定到 500 个差异蛋白（表 S5）。严格条件下，筛选标准为 $FC \geq 2$ 或 ≤ 0.5，双尾非配对 t 检验 $P < 0.01$，可以鉴定到 108 个差异蛋白（表 S6）。Yuan Zhang 等人[72]提出，生长激素分泌物受体系统(The Growth Hormone Secretagogue Receptor System)参与了芍药苷快速而持续的抗抑郁作用。

将宽松条件下双相组与抑郁组鉴定到的差异蛋白进行功能分析，共富集到细胞粘附、补体激活经典途径、通过质膜粘附分子的嗜同性细胞粘附等 162 个生物学过程和补体和凝血级联反应、肌动蛋白细胞骨架调节等 27 个信号通路（表 S7）。其中大部分生物学过程和信号通路与免疫系统相关，这一特点同样可以体现在抑郁症单例样本与健康组相比筛选的差异蛋白富集到的生物学过程和信号通路结果中。

3.1.2 非监督聚类分析

将健康组与双相组所鉴定到的全蛋白进行非监督聚类分析，可见大部分双相情感障碍患者样本可以很好的与健康组分开（图 2）。而将健康组与抑郁组所鉴定到的全蛋白进行非监督聚类分析可知，基本上抑郁症患者样本能够与健康组彻底分开，但仍存在部分抑郁症患者样本与健康人样本更为接近的现象（图 3）。这说明尿液蛋白质组可以显著区分健康人与抑郁症患者，相较于传统的心理量表，能够为抑郁症的诊断提供有力的客观指标。并且证明尿液蛋白质组可能存在反映抑郁症疾病阶段的潜力，相较于与健康人样本差异更大的抑郁症样本，与健康人样本更为接近的抑郁症样本可能症状较轻，处于抑郁症初级阶段。当我们将抑郁组与双相组鉴定到的全蛋白进行非监督聚类分析时，发现双相患者样本与部分抑郁症患者

样本更为一致，而与另外一部分抑郁症患者样本能够很好的区分开（图 4）。我们推测可能与双相患者样本更为相似的抑郁症患者样本具有潜在转变为双相情感障碍的可能性，或许能够为患者未来的用药提供一些指导性意见。

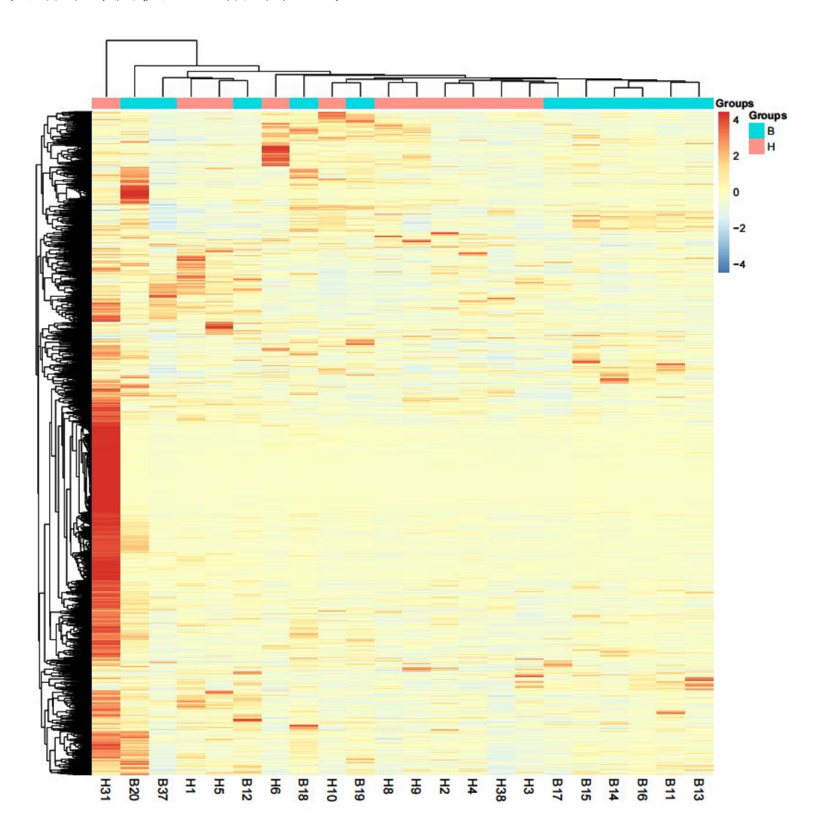


图 2 健康组与双相组的全蛋白非监督聚类热图

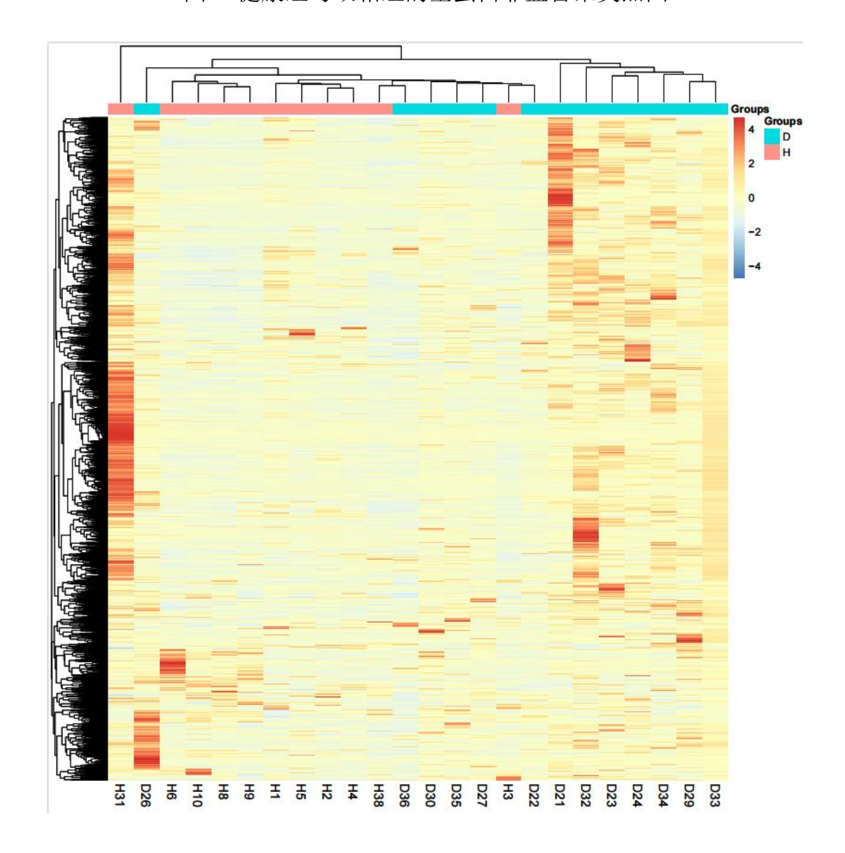


图 3 健康组与抑郁组的全蛋白非监督聚类热图

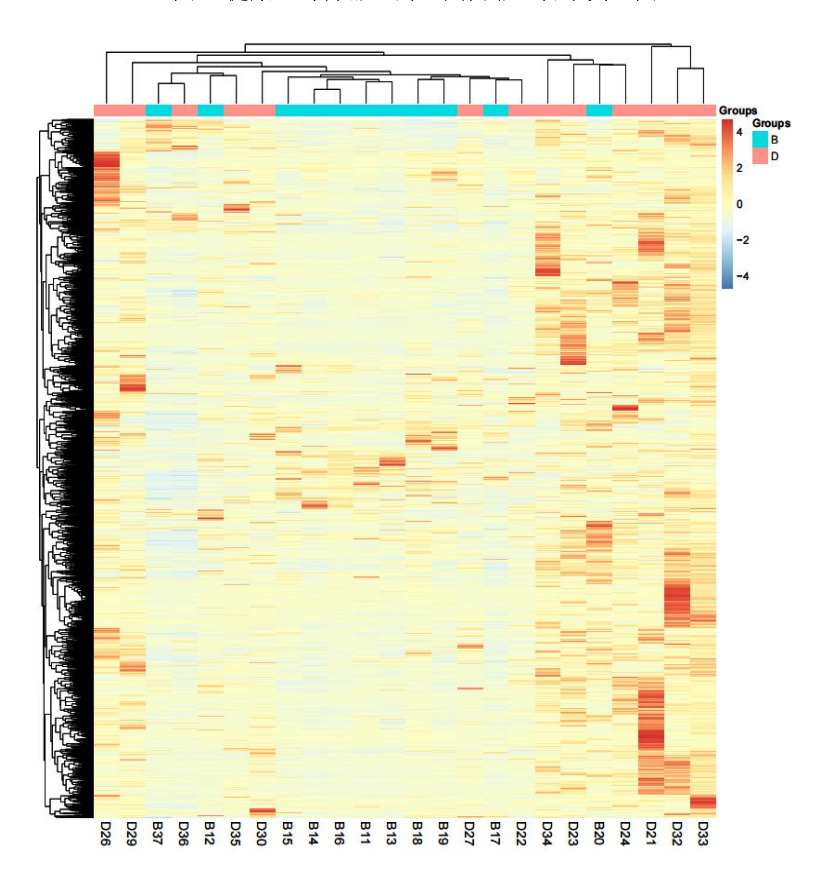


图 4 双相组与抑郁组的全蛋白非监督聚类热图

3.1.3 随机分组检验

为了确定鉴定到的差异蛋白是随机产生的可能性，将随机取 10 例健康人样本和随机取 10 例双相患者样本鉴定到的总蛋白进行随机分组验证（FC≥1.5 或≤0.67，P<0.05），产生的差异蛋白平均为 41.0 个，表明至少有 32.9%的差异蛋白不是随机产生的（表 4）；以较为严格的条件（FC≥2 或≤0.5，P<0.01）进行随机分组验证，产生的差异蛋白平均为 2.7 个，表明至少有 60.8%的差异蛋白不是随机产生的（表 4）。将随机取 10 例健康人样本和随机取 10 例抑郁患者样本鉴定到的总蛋白进行随机分组验证（FC≥1.5 或≤0.67，P<0.05），产生的差异蛋白平均为 54.7 个，表明至少有 80.2%的差异蛋白不是随机产生的（表 4）；以较为严格的条件（FC≥2 或≤0.5，P<0.01）进行随机分组验证，产生的差异蛋白平均为 4.4 个，表明至少有 92.7%的差异蛋白不是随机产生的（表 4）。将随机取 10 例双相患者样本和随机取 10 例抑郁患者样本鉴定到的总蛋白进行随机分组验证（FC≥1.5 或≤0.67，P<0.05），产生的差异蛋白平均为 53.4 个，表明至少有 89.3%的差异蛋白不是随机产生的（表 4）；以较为严格的条件（FC≥2 或≤0.5，P<0.01）进行随机分组验证，产生的差异蛋白平均为 3.7 个，表明至少有 96.6%的差异蛋白不是随机产生的（表 4）。

通过对比不同组随机产生的差异蛋白比例可知，健康人样本与双相患者样本产生的差异显著性较小，健康人样本与抑郁患者样本产生的差异显著性较大，而双相患者样本与抑郁患者样本产生的差异显著性较大，可信度最高。

表 4 随机分组结果

分组	差异蛋白筛选条件	差异蛋白数量	随机产生的差异蛋白数量	可信差异蛋白占比

健康 vs	FC≥1.5 或≤0.67; P<0.05	67	41.0	32.9 %
双相	FC≥2 或≤0.5; P<0.01	7	2.7	60.8 %
健康 vs	FC≥1.5 或≤0.67; P<0.05	276	54.7	80.2 %
抑郁	FC≥2 或≤0.5; P<0.01	61	4.4	92.7 %
双相 vs	FC≥1.5 或≤0.67; P<0.05	500	53.4	89.3 %
抑郁	FC≥2 或≤0.5; P<0.01	108	3.7	96.6 %

3.2 一对多尿液蛋白质组的变化分析

为了更好的判断双相组和抑郁组每一例患者的疾病情况，达到精准治疗的效果，我们将单例患者样本与健康组 11 例样本进行一对多的比较分析。

3.2.1 尿液蛋白质组的鉴定

将双相组 11 例样本分别与健康组相比较，宽松条件下筛选到的差异蛋白及其表达趋势如表 5 所示。将抑郁组 13 例样本分别与健康组相比较，宽松条件下筛选到的差异蛋白及其表达趋势如表 5 所示。通过对比两组结果我们发现，单例抑郁症患者样本与健康组相比筛选到的差异蛋白数量普遍大于单例双相情感障碍患者的样本，说明抑郁症患者呈现出与健康人相当显著的差异，这一现象符合成组分析中非监督聚类分析的结果。

表 5 双相组单例样本和抑郁组单例样本与健康组相比的差异蛋白的表达变化（FC≥1.5 或≤0.67，P<0.05）

分组	差异蛋白表达趋势	样本号												
		1	2	3	4	5	6	7	8	9	10	11	12	13
健康/双相	Total	122	146	173	155	154	120	167	192	160	274	252	-	-
	↑	78	92	92	82	98	74	67	143	97	225	98	-	-
	↓	44	54	81	73	56	46	100	49	63	49	154	-	-
健康/抑郁	Total	813	670	698	678	706	685	554	675	749	684	682	676	660
	↑	674	413	561	521	550	383	375	420	554	437	473	387	334
	↓	139	257	137	157	156	302	179	255	195	247	209	289	326

3.2.2 双相组单例样本和抑郁组单例样本与健康组相比共有的差异蛋白分析

为了探究 11 例双相情感障碍患者之间是否存在共同的差异蛋白，我们将双相组单例样本与健康组相比在宽松条件下筛选到的差异蛋白进行 Venn 图分析，可以发现有 4 个差异蛋白被 11 例中的 8 例双相患者样本共同筛选到，且呈现出较为一致的表达变化趋势；有 9 个差异蛋白被 7 例双相患者样本共同筛选到（表 6）。Yachen Shi 等人[73]在血浆中鉴定到了重度抑郁症患者的抗凝血酶 III(Antithrombin-III, AT III)表达水平均显著升高，被列为候选生物标志物。2021 年 Cem Cerit 等人[74]发现 AMBP 蛋白的强度可区分 BD 患者躁狂发作与缓解期和健康对照，表明 AMBP 蛋白可能是 BD 患者躁狂发作的候选生物标志物。

将抑郁组单例样本与健康组相比在宽松条件下筛选到的差异蛋白进行 Venn 图分析，可以发现有 24 个差异蛋白被 13 例抑郁患者样本共同筛选到，其中的 16 个差异蛋白在 13 例抑郁患者中呈现出完全一致的表达变化趋势（表 6），且其中有 6 个差异蛋白与免疫球蛋白有关(Immunoglobulin)；有 41 个差异蛋白被 13 例中的 12 例抑郁患者样本共同筛选到（表 S8），且其中的 19 个差异蛋白在 12 例抑郁患者中呈现出完全一致的表达变化趋势（表 6），这些结果均反映出了极强的一致性。值得一提的是，在双相组和抑郁组中，我们均筛选到了骨桥蛋白(Osteopontin, OPN)，骨桥蛋白是参与神经炎症的关键分子之一[75]，Tingting Li 等人[76]

的研究表明，阻断骨桥蛋白表达可减轻神经炎症，减轻骨桥蛋白在脂多糖诱导的小鼠抑郁样行为。Kadriu, B.等人[77]研究发现，重度抑郁症患者血浆中的 OPN 水平显著降低。Lee H 等人[78]在血浆中筛选到了和抑郁症症状（如快感缺失/迟缓）严重程度呈明显相关性的生物标志物：甘露结合凝集素丝氨酸蛋白酶 2(Mannan-binding lectin serine protease 2, MASP2)，且同样富集到了补体激活途径，这与本文的结果相匹配。肿瘤坏死因子(Tumor necrosis factor, TNF)超家族成员因与炎症和神经发生的关系，在神经精神疾病的发病机制中发挥作用，TNF 等促炎因子的增加可能是重度抑郁障碍中低度炎症的典型表现[79]。

表 6 双相组单例样本和抑郁组单例样本与健康组相比共有的差异蛋白（FC≥1.5 或≤0.67，P<0.05）

双相组			抑郁组		
差异蛋白编号	差异蛋白名称	差异蛋白变化趋势	差异蛋白编号	差异蛋白名称	差异蛋白变化趋势
P10451	Osteopontin	1↑7↓	P10451	Osteopontin	13↓
O60293	Zinc finger C3H1 domain-containing protein	1↑7↓	-	-	-
O95967	EGF-containing fibulin-like extracellular matrix protein 2	1↑7↓	-	-	-
P26842	CD27 antigen	2↑6↓	-	-	-
P01008	Antithrombin-III	7↑	-	-	-
C9IZ46	Protein shisa-5	7↓	-	-	-
P02760	Protein AMBP	7↓	-	-	-
Q9BVM4	Gamma-glutamylaminecyclotransferase	1↑6↓	-	-	-
P61970	Nuclear transport factor 2	1↑6↓	-	-	-
P98164	Low-density lipoprotein receptor-related protein 2	5↑2↓	-	-	-
A0A075B6R9	Probable non-functional immunoglobulin kappa variable 2D-24	2↑5↓	-	-	-
P48061	Stromal cell-derived factor 1	5↑2↓	-	-	-
Q9H1C7	Cysteine-rich and transmembrane domain-containing protein 1	4↑3↓	-	-	-
-	-	-	Q96IQ7	V-set and immunoglobulin domain-containing protein 2	13↑
-	-	-	P0DOX5	Immunoglobulin gamma-1 heavy chain	13↓
-	-	-	A0A075B6S2	Immunoglobulin kappa variable 2D-29	13↓
-	-	-	P01833	Polymeric immunoglobulin receptor	13↓
-	-	-	O00187	Mannan-binding lectin serine protease 2	13↓
-	-	-	P50591	Tumor necrosis factor ligand superfamily member 10	13↓
-	-	-	P01859	Immunoglobulin heavy constant gamma 2	13↓
-	-	-	P01834	Immunoglobulin kappa constant	13↓

-	-	-	P10153	Non-secretory ribonuclease	13↓
-	-	-	C9IZ46	Protein shisa-5	13↓
-	-	-	O75339	Cartilage intermediate layer protein 1	13↓
-	-	-	Q96FE7	Phosphoinositide-3-kinase-interacting protein 1	13↓
-	-	-	P07998	Ribonuclease pancreatic	13↓
-	-	-	P01009	Alpha-1-antitrypsin	13↓
-	-	-	P01042	Kininogen-1	13↓
-	-	-	A0A087X0K0	Collagen type XV alpha 1 chain	2↑11↓
-	-	-	P10253	Lysosomal alpha-glucosidase	2↑11↓
-	-	-	P15328	Folate receptor alpha	2↑11↓
-	-	-	P00734	Prothrombin	2↑11↓
-	-	-	Q8WZ75	Roundabout homolog 4	2↑11↓
-	-	-	B8ZZQ6	Prothymosin alpha	2↑11↓
-	-	-	P02790	Hemopexin	2↑11↓
-	-	-	A0A2R8Y478	CD9 molecule	7↑6↓

为了进一步探究抑郁组单例样本与健康组相比呈现出的一致性差异，我们将 12 例及以上抑郁患者样本共同筛选到的 65 个差异蛋白进行功能分析，共富集到了补体激活经典途径、视网膜稳态、适应性免疫应答、细胞粘附等 25 个生物学过程，其中大部分均与免疫系统相关（表 7），同时我们还富集到了补体和凝血级联反应这一信号通路（P<0.05）。免疫机制可能是重度抑郁症的发病机制之一，而具有主要免疫靶点的药物可以改善抑郁症状[80]。本文的结果无疑再次印证了抑郁症与免疫系统之间的相关性，或许可通过观测抑郁症患者机体的免疫状态对精准治疗抑郁症提供方向和依据。这一结果也反映了尿蛋白质组可以为治疗抑郁症与双相情感障碍提出可能的机制和潜在的靶点，为今后疾病的鉴别诊断及精准治疗提供了工具。

表 7 抑郁组单例样本与健康组相比 12 例及以上共有的差异蛋白富集到的生物学过程（P<0.05）

Term	P-Value
complement activation, classical pathway	3.60E-06
retina homeostasis	1.20E-05
adaptive immune response	1.80E-05
cell adhesion	9.30E-05
positive regulation of B cell activation	3.10E-04
phagocytosis, recognition	3.30E-04
phagocytosis, engulfment	5.80E-04
antimicrobial humoral immune response mediated by antimicrobial peptide	6.40E-04
B cell receptor signaling pathway	1.10E-03
innate immune response	1.10E-03
defense response to bacterium	1.70E-03
antibacterial humoral response	2.00E-03
negative regulation of proteolysis	2.60E-03
blood coagulation	3.60E-03

immune response	6.50E-03
signal transduction	9.90E-03
defense response to Gram-positive bacterium	1.10E-02
hemoglobin metabolic process	1.60E-02
RNA phosphodiester bond hydrolysis	2.00E-02
receptor-mediated endocytosis	2.70E-02
cobalamin transport	2.90E-02
immunoglobulin mediated immune response	3.30E-02
cobalamin metabolic process	3.90E-02
sperm-egg recognition	4.20E-02
negative regulation of peptidase activity	4.50E-02

4. 结论

本研究发现了抑郁症和双相情感障碍的尿蛋白质组差异，印证了抑郁症与免疫系统之间的相关性，这一结果和以往的研究一致：免疫机制可能是重度抑郁症的发病机制之一，而具有主要免疫靶点的药物可以改善抑郁症状。未来或许可通过观测抑郁症患者机体的免疫状态对精准治疗抑郁症提供方向和依据。本文研究结果显示尿液蛋白质组可以鉴别诊断抑郁症与双相情感障碍，为治疗抑郁症与双相情感障碍提出可能的机制和潜在的靶点，为今后疾病的鉴别诊断及精准治疗提供了工具。

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附表：

表 S1 健康人与双相患者相比的差异蛋白 (FC≥1.5 或≤0.67, P<0.05)

Accession	Protein names	Trend	FC	P-Value
A0A0C4ZNX3	Killer cell immunoglobulin-like receptor	↓	0.28	2.92E-02
O15511	Actin-related protein 2/3 complex subunit 5	↓	0.37	3.32E-02
Q96C23	Galactose mutarotase	↓	0.43	7.19E-04
C9IZ46	Protein shisa-5	↓	0.43	1.67E-03
O43852	Calumenin	↓	0.47	4.54E-03
P14174	Macrophage migration inhibitory factor	↓	0.48	1.24E-02
O95388	CCN family member 4	↓	0.49	3.98E-02
P15121	Aldo-keto reductase family 1 member B1	↓	0.50	4.58E-02
P32942	Intercellular adhesion molecule 3	↓	0.51	1.37E-03
O95967	EGF-containing fibulin-like extracellular matrix protein 2	↓	0.51	1.81E-04
P21695	Glycerol-3-phosphate dehydrogenase	↓	0.53	4.89E-02
Q8N386	Leucine-rich repeat-containing protein 25	↓	0.54	9.40E-03
P00918	Carbonic anhydrase 2	↓	0.56	2.09E-02
P83110	Serine protease HTRA3	↓	0.57	3.84E-02
A6NI73	Leukocyte immunoglobulin-like receptor subfamily A member 5	↓	0.58	1.90E-03
O95297	Myelin protein zero-like protein 1	↓	0.62	2.48E-02
P35555	Fibrillin-1 [Cleaved into: Asprosin]	↓	0.62	3.20E-02
Q9BVM4	Gamma-glutamylaminecyclotransferase	↓	0.64	1.28E-02
A0A087X0K0	Collagen type XV alpha 1 chain	↓	0.64	2.82E-02
O60704	Protein-tyrosine sulfotransferase 2	↓	0.64	2.60E-02
O94760	Dimethylarginine dimethylaminohydrolase 1	↓	0.64	7.44E-03
P78417	Glutathione S-transferase omega-1	↓	0.65	3.38E-02
P36955	Pigment epithelium-derived factor	↓	0.65	2.37E-02
Q9Y5E4	Protocadherin beta-5	↓	0.65	5.03E-03
P15328	Folate receptor alpha	↓	0.66	5.69E-03
P29279	CCN family member 2	↓	0.67	2.04E-02
P08582	Melanotransferrin	↓	0.67	2.77E-02
Q86UD1	Out at first protein homolog	↑	1.50	3.72E-02
Q6EMK4	Vasorin	↑	1.52	4.06E-02
Q9H3G5	Probable serine carboxypeptidase CPVL	↑	1.52	4.57E-02
P30047	GTP cyclohydrolase 1 feedback regulatory protein	↑	1.52	4.10E-02
A8MTF8	FAM3 metabolism regulating signaling molecule B	↑	1.52	2.14E-02
Q8IV08	5'-3' exonuclease PLD3	↑	1.55	4.71E-02
Q9H1C7	Cysteine-rich and transmembrane domain-containing protein 1	↑	1.56	3.56E-02
P00338	L-lactate dehydrogenase A chain	↑	1.57	4.76E-02
P01008	Antithrombin-III	↑	1.58	1.04E-02
E9PHN6	Glutathione S-transferase	↑	1.58	4.46E-02
O43493	Trans-Golgi network integral membrane protein 2	↑	1.59	2.60E-02
P25774	Cathepsin S	↑	1.60	4.19E-02

Q92743	Serine protease HTRA1	↑	1.60	2.95E-02
P10619	Lysosomal protective protein	↑	1.61	4.08E-02
O43505	Beta-1,4-glucuronyltransferase 1	↑	1.64	8.96E-03
P48061	Stromal cell-derived factor 1	↑	1.65	1.17E-02
O43895	Xaa-Pro aminopeptidase 2	↑	1.65	3.23E-02
O95445	Apolipoprotein M	↑	1.68	1.15E-03
P01009	Alpha-1-antitrypsin	↑	1.68	2.92E-02
Q08380	Galectin-3-binding protein	↑	1.69	3.35E-02
Q14314	Fibroleukin	↑	1.71	4.73E-02
E9PMR4	Tetraspanin	↑	1.72	3.37E-02
P01019	Angiotensinogen	↑	1.75	4.72E-03
P12821	Angiotensin-converting enzyme	↑	1.77	2.23E-02
P0C7U0	Protein ELFN1	↑	1.78	1.64E-02
C9JXF9	Insulin-like growth factor-binding protein 1	↑	1.81	2.60E-02
Q9UBD6	Ammonium transporter Rh type C	↑	1.84	3.42E-02
Q1EHB4	Sodium-coupled monocarboxylate transporter 2	↑	1.90	1.93E-02
A0A087WYX9	Collagen type V alpha 2 chain	↑	1.90	5.47E-03
P49006	MARCKS-related protein	↑	1.93	1.83E-02
P12724	Eosinophil cationic protein	↑	1.99	3.68E-02
P10451	Osteopontin	↑	2.00	7.75E-03
Q92820	Gamma-glutamyl hydrolase	↑	2.14	2.14E-02
P05154	Plasma serine protease inhibitor	↑	2.14	1.43E-02
P01024	Complement C3	↑	2.16	2.11E-02
E7EMR3	Adhesion G protein-coupled receptor L3	↑	2.33	1.38E-02
O60293	Zinc finger C3H1 domain-containing protein	↑	2.36	8.18E-04
O95433	Activator of 90 kDa heat shock protein ATPase homolog 1	↑	2.40	8.47E-06
O00144	Frizzled-9	↑	2.42	2.11E-02
P08473	Neprilysin	↑	2.55	1.33E-03

表 S2 宽松条件下健康组与双相组相比产生的差异蛋白富集到的生物学过程和信号通路(P<0.05)

BP	P-Value	Pathway	P-Value
negative regulation of endopeptidase activity	3.10E-05	Renin-angiotensin system	1.50E-04
proteolysis	5.60E-05	Complement and coagulation cascades	7.10E-03
cell adhesion	7.00E-05	Protein digestion and absorption	1.20E-02
aging	1.00E-04	-	-
ossification	2.30E-03	-	-
positive regulation of protein tyrosine kinase activity	4.10E-03	-	-
positive regulation of neurogenesis	4.70E-03	-	-
positive regulation of inflammatory response	5.10E-03	-	-
regulation of renal output by angiotensin	6.40E-03	-	-
kidney development	6.40E-03	-	-
signal transduction	7.10E-03	-	-
substance P catabolic process	9.60E-03	-	-
hormone catabolic process	1.30E-02	-	-
positive regulation of cell activation	1.30E-02	-	-
negative regulation of gene expression	1.70E-02	-	-
regulation of systemic arterial blood pressure by renin-angiotensin	1.90E-02	-	-
bradykinin catabolic process	2.20E-02	-	-
cellular oxidant detoxification	2.30E-02	-	-
positive regulation of ryanodine-sensitive calcium-release channel activity	2.80E-02	-	-
negative regulation of ryanodine-sensitive calcium-release channel activity	3.50E-02	-	-
angiotensin-activated signaling pathway	3.80E-02	-	-
beta-amyloid clearance	4.10E-02	-	-
beta-amyloid metabolic process	4.10E-02	-	-
negative regulation of transforming growth factor beta receptor signaling pathway	4.10E-02	-	-
response to acidic pH	4.40E-02	-	-
negative regulation of defense response to virus	4.70E-02	-	-

表 S3 健康人与抑郁患者相比的差异蛋白 (FC≥1.5 或≤0.67, P<0.05)

Accession	Protein names	Trend	FC	P-Value
A0A182DWH7	Selenoprotein P	↓	0.44	1.36E-02
P15328	Folate receptor alpha	↓	0.44	4.95E-05
P68104	Elongation factor 1-alpha 1	↓	0.48	1.64E-02
A0A2R8Y5S7	Radixin	↓	0.55	1.52E-03
Q8WUM4	Programmed cell death 6-interacting protein	↓	0.57	4.98E-03
C9IZ46	Protein shisa-5	↓	0.58	1.14E-02
P14618	Pyruvate kinase PKM	↓	0.59	2.67E-02
P26038	Moesin	↓	0.60	4.89E-02
Q6PK18	2-oxoglutarate and iron-dependent oxygenase domain-containing protein 3	↓	0.60	1.28E-02
F8VNT9	CD63 molecule	↓	0.62	1.04E-02
Q96C23	Galactose mutarotase	↓	0.62	8.13E-03
A0A087X0K0	Collagen type XV alpha 1 chain	↓	0.63	1.96E-02
Q9UNZ2	NSFL1 cofactor p47	↓	0.65	4.68E-02
P61970	Nuclear transport factor 2	↓	0.65	4.03E-03
P00734	Prothrombin	↓	0.65	3.06E-02
A6NI73	Leukocyte immunoglobulin-like receptor subfamily A member 5	↓	0.66	5.40E-03
O00115	Deoxyribonuclease-2-alpha	↓	0.67	4.95E-02
P18206	Vinculin	↑	1.50	4.02E-02
P07204	Thrombomodulin	↑	1.50	8.00E-04
A0A3B3ISV3	Collagen type IV alpha 1 chain	↑	1.51	1.26E-02
A0A075B6R2	Immunoglobulin heavy variable 4-4	↑	1.52	2.69E-02
P28799	Progranulin	↑	1.52	1.98E-02
P24593	Insulin-like growth factor-binding protein 5	↑	1.53	2.74E-02
P05362	Intercellular adhesion molecule 1	↑	1.53	2.76E-02
Q14376	UDP-glucose 4-epimerase	↑	1.53	2.52E-02
P51148	Ras-related protein Rab-5C	↑	1.54	4.54E-02
Q68D85	Natural cytotoxicity triggering receptor 3 ligand 1	↑	1.54	2.16E-02
Q92692	Nectin-2	↑	1.54	9.85E-03
A0A1B0GU58	Propionyl-CoA carboxylase alpha chain, mitochondrial	↑	1.54	2.83E-02
P0DOX5	Immunoglobulin gamma-1 heavy chain	↑	1.54	1.98E-02
E5RIW3	Tubulin-specific chaperone A	↑	1.55	3.68E-02
P07711	Procathepsin L	↑	1.55	1.69E-02
P39060	Collagen alpha-1	↑	1.56	2.60E-02
P78324	Tyrosine-protein phosphatase non-receptor type substrate 1	↑	1.57	4.09E-02
A0A0A0MS15	Immunoglobulin heavy variable 3-49	↑	1.58	3.27E-02
J3QQX6	Intercellular adhesion molecule 2	↑	1.59	2.10E-03
Q15907	Ras-related protein Rab-11B	↑	1.59	7.48E-03
P55957	BH3-interacting domain death agonist	↑	1.59	1.44E-02
E7ES19	Thrombospondin 4	↑	1.60	3.70E-02
P11362	Fibroblast growth factor receptor 1	↑	1.62	1.85E-02

A0A087X0T8	Cell adhesion molecule 1	↑	1.64	2.59E-03
P08571	Monocyte differentiation antigen CD14	↑	1.65	4.61E-02
H3BP20	Beta-hexosaminidase	↑	1.65	2.26E-02
A8MTF8	FAM3 metabolism regulating signaling molecule B	↑	1.66	2.47E-02
P02760	Protein AMBP	↑	1.66	4.78E-02
P13671	Complement component C6	↑	1.66	1.81E-02
B8ZZ73	Interleukin 1 receptor type 1	↑	1.67	2.51E-02
P15169	Carboxypeptidase N catalytic chain	↑	1.68	4.97E-03
Q6UX71	Plexin domain-containing protein 2	↑	1.68	2.00E-02
Q496F6	CMRF35-like molecule 2	↑	1.68	2.94E-02
P25325	3-mercaptopyruvate sulfurtransferase	↑	1.69	4.70E-02
O43505	Beta-1,4-glucuronyltransferase 1	↑	1.70	9.66E-03
P27797	Calreticulin	↑	1.70	2.63E-02
Q9H756	Leucine-rich repeat-containing protein 19	↑	1.70	2.39E-02
P02753	Retinol-binding protein 4	↑	1.71	3.13E-02
P04004	Vitronectin	↑	1.71	1.99E-02
Q9NUM4	Transmembrane protein 106B	↑	1.72	4.39E-02
O14773	Tripeptidyl-peptidase 1	↑	1.75	2.54E-02
A0A075B6S2	Immunoglobulin kappa variable 2D-29	↑	1.75	3.89E-02
Q92820	Gamma-glutamyl hydrolase	↑	1.75	5.11E-03
P48061	Stromal cell-derived factor 1	↑	1.75	4.22E-02
Q5JS37	NHL repeat-containing protein 3	↑	1.76	3.01E-03
Q9NPG4	Protocadherin-12	↑	1.76	8.40E-03
M0QZG5	CD209 antigen, isoform CRA_j	↑	1.76	2.70E-02
O75339	Cartilage intermediate layer protein 1	↑	1.77	3.22E-02
P01834	Immunoglobulin kappa constant	↑	1.77	8.37E-03
Q16769	Glutaminyl-peptide cyclotransferase	↑	1.78	2.03E-02
K3W4U1	Fc epsilon receptor II	↑	1.78	2.81E-02
Q12864	Cadherin-17	↑	1.78	4.84E-02
P01859	Immunoglobulin heavy constant gamma 2	↑	1.78	1.26E-02
P00450	Ceruloplasmin	↑	1.79	3.16E-02
J3KPQ0	Fibroblast growth factor receptor	↑	1.80	2.32E-02
P19961	Alpha-amylase 2B	↑	1.80	2.34E-02
Q9H461	Frizzled-8	↑	1.81	4.49E-04
P20933	N(4)-(beta-N-acetylglucosaminyl)-L-asparaginase	↑	1.83	2.50E-02
P02749	Beta-2-glycoprotein 1	↑	1.85	2.12E-02
A0A087WTY6	Neuroblastoma suppressor of tumorigenicity 1	↑	1.85	4.84E-04
A0A0C4DH38	Immunoglobulin heavy variable 5-51	↑	1.85	2.88E-02
Q96IU4	Putative protein-lysine deacylase ABHD14B	↑	1.86	5.27E-03
A0A087WX80	Laminin subunit alpha 2	↑	1.87	3.06E-02
Q02413	Desmoglein-1	↑	1.87	9.15E-03
P48745	CCN family member 3	↑	1.88	2.09E-02
P10253	Lysosomal alpha-glucosidase	↑	1.88	6.66E-03

Q96GW7	Brevican core protein	↑	1.89	2.02E-02
Q9UFM8	Neuroplastin	↑	1.89	4.48E-02
P55000	Secreted Ly-6/uPAR-related protein 1	↑	1.90	2.68E-03
A0A0C4DFZ2	Arylsulfatase A	↑	1.91	8.68E-03
P10619	Lysosomal protective protein	↑	1.92	1.21E-02
P20674	Cytochrome c oxidase subunit 5A, mitochondrial	↑	1.92	2.42E-02
Q9H6B4	CXADR-like membrane protein	↑	1.94	2.61E-02
A8MW49	Fatty acid-binding protein, liver	↑	1.95	9.39E-03
A0A0A0MQS9	Laminin subunit alpha 4	↑	1.96	3.60E-02
A0A0U1RQC5	Neurexin 3	↑	1.97	2.34E-02
Q8NFT8	Delta and Notch-like epidermal growth factor-related receptor	↑	1.97	1.22E-02
P22792	Carboxypeptidase N subunit 2	↑	1.98	8.60E-04
A0A0C4DH43	Immunoglobulin heavy variable 2-70D	↑	1.99	9.02E-03
A6NC48	ADP-ribosyl cyclase/cyclic ADP-ribose hydrolase	↑	1.99	6.40E-03
Q9Y646	Carboxypeptidase Q	↑	1.99	3.83E-03
Q9Y376	Calcium-binding protein 39	↑	2.01	1.42E-02
O95445	Apolipoprotein M	↑	2.03	4.56E-03
P02774	Vitamin D-binding protein	↑	2.03	1.64E-02
P01210	Proenkephalin-A	↑	2.07	7.08E-03
Q5T123	SH3 domain-binding glutamic acid-rich-like protein 3	↑	2.08	3.02E-02
P08473	Neprilysin	↑	2.09	2.87E-02
A0A096LP69	CD99 molecule	↑	2.09	2.29E-02
P10109	Adrenodoxin, mitochondrial	↑	2.09	3.44E-02
Q13113	PDZK1-interacting protein 1	↑	2.10	6.97E-03
P50591	Tumor necrosis factor ligand superfamily member 10	↑	2.10	9.61E-03
O43493	Trans-Golgi network integral membrane protein 2	↑	2.10	2.28E-03
P14151	L-selectin	↑	2.12	4.79E-03
Q9HB75	p53-induced death domain-containing protein 1	↑	2.15	7.11E-03
A0A0G2JNI0	Transmembrane protease serine	↑	2.17	4.90E-02
O96009	Napsin-A	↑	2.17	3.54E-02
P30047	GTP cyclohydrolase 1 feedback regulatory protein	↑	2.19	7.16E-03
P01024	Complement C3	↑	2.19	4.47E-02
Q14019	Coactosin-like protein	↑	2.21	1.10E-02
P31025	Lipocalin-1	↑	2.22	9.26E-03
O95841	Angiopoietin-related protein 1	↑	2.23	1.58E-02
P02787	Serotransferrin	↑	2.23	4.56E-02
P01011	Alpha-1-antichymotrypsin	↑	2.24	1.09E-02
Q13443	Disintegrin and metalloproteinase domain-containing protein 9	↑	2.27	4.49E-02
P32320	Cytidine deaminase	↑	2.27	4.55E-02
P04196	Histidine-rich glycoprotein	↑	2.27	6.06E-03
P07437	Tubulin beta chain	↑	2.32	3.34E-02
P05556	Integrin beta-1	↑	2.33	1.44E-02

Q9UJ72	Annexin A10	↑	2.33	4.24E-02
P32004	Neural cell adhesion molecule L1	↑	2.35	2.14E-02
O00592	Podocalyxin	↑	2.36	2.86E-02
B1APH0	Basonuclin 2	↑	2.36	1.97E-02
A0A087WYX9	Collagen type V alpha 2 chain	↑	2.37	1.38E-03
P01111	GTPase NRas	↑	2.38	1.91E-02
A0A3B3IUC4	Alpha-galactosidase	↑	2.38	4.72E-02
Q68CJ9	Cyclic AMP-responsive element-binding protein 3-like protein 3	↑	2.38	3.32E-03
Q86TY3	Armadillo-like helical domain-containing protein 4	↑	2.39	8.94E-03
P25391	Laminin subunit alpha-1	↑	2.40	2.17E-02
G5E9G7	Neurexin 2	↑	2.41	1.84E-02
O75487	Glypican-4	↑	2.42	3.92E-02
I3L0L6	E3 ubiquitin-protein ligase RNF167	↑	2.43	4.72E-02
P12830	Cadherin-1	↑	2.43	1.26E-02
P49788	Retinoic acid receptor responder protein 1	↑	2.44	1.14E-02
A0A3B3IRL2	Cellular repressor of E1A stimulated genes 1	↑	2.48	2.31E-02
A0A087WZW1	Colipase	↑	2.54	6.76E-03
A0A0J9YX35	Immunoglobulin heavy variable 3-64D	↑	2.55	4.92E-03
K7EKI0	Envoplakin	↑	2.55	3.19E-02
A0A286YFJ8	Immunoglobulin heavy constant gamma 4	↑	2.57	2.05E-02
P29401	Transketolase	↑	2.60	3.61E-02
P49006	MARCKS-related protein	↑	2.66	3.09E-02
P01178	Oxytocin-neurophysin 1	↑	2.66	8.71E-04
P06858	Lipoprotein lipase	↑	2.68	4.66E-02
O94919	Endonuclease domain-containing 1 protein	↑	2.68	5.88E-04
P01019	Angiotensinogen	↑	2.69	1.67E-02
P30046	D-dopachrome decarboxylase	↑	2.70	2.46E-02
Q14118	Dystroglycan 1	↑	2.71	3.33E-03
P06731	Carcinoembryonic antigen-related cell adhesion molecule 5	↑	2.74	2.32E-02
Q9Y4D7	Plexin-D1	↑	2.74	2.14E-02
P02765	Alpha-2-HS-glycoprotein	↑	2.75	3.22E-03
Q86UD1	Out at first protein homolog	↑	2.79	7.73E-03
Q92626	Peroxidasin homolog	↑	2.82	9.41E-03
P28072	Proteasome subunit beta type-6	↑	2.82	4.29E-02
F5H0U5	Glycolipid transfer protein	↑	2.86	8.92E-03
P16989	Y-box-binding protein 3	↑	2.87	4.64E-03
P11766	Alcohol dehydrogenase class-3	↑	2.88	1.87E-04
H3BMA1	Mesothelin	↑	2.88	4.37E-02
P12318	Low affinity immunoglobulin gamma Fc region receptor II-a	↑	2.89	9.59E-03
A0A1B0GTG2	Aldehyde dehydrogenase 7 family member A1	↑	2.89	1.63E-02
P27348	14-3-3 protein theta	↑	2.91	1.20E-02
M0QYN0	Myeloid derived growth factor	↑	2.93	4.53E-02

Q6PI73	Leukocyte immunoglobulin-like receptor subfamily A member 6	↑	2.94	1.49E-02
A0A0G2JSC0	Immunoglobulin lambda variable 5-45	↑	2.94	3.71E-03
P29692	Elongation factor 1-delta	↑	2.96	7.19E-04
Q9BY89	Uncharacterized protein KIAA1671	↑	2.96	2.67E-02
P54826	Growth arrest-specific protein 1	↑	2.97	5.66E-03
Q8N8N7	Prostaglandin reductase 2	↑	2.98	4.54E-02
Q92496	Complement factor H-related protein 4	↑	3.01	6.77E-04
Q16348	Solute carrier family 15 member 2	↑	3.03	3.53E-02
P48304	Lithostathine-1-beta	↑	3.11	3.93E-02
P17655	Calpain-2 catalytic subunit	↑	3.12	1.77E-03
Q7Z794	Keratin, type II cytoskeletal 1b	↑	3.15	5.08E-03
P22304	Iduronate 2-sulfatase	↑	3.17	6.17E-03
P30044	Peroxiredoxin-5	↑	3.20	4.60E-03
Q9UJ99	Cadherin-22	↑	3.23	4.90E-02
B7Z4G8	Amyloid beta precursor like protein 1	↑	3.24	4.41E-02
C9JM33	Interferon alpha and beta receptor subunit 2	↑	3.25	1.82E-02
P52961	GPI-linked NAD	↑	3.28	2.00E-02
Q5T2L0	V-set domain containing T cell activation inhibitor 1	↑	3.29	2.81E-02
P68371	Tubulin beta-4B chain	↑	3.39	2.01E-03
P36941	Tumor necrosis factor receptor superfamily member 3	↑	3.40	3.00E-02
A0A0C4DH72	Immunoglobulin kappa variable 1-6	↑	3.41	2.75E-03
P68363	Tubulin alpha-1B chain	↑	3.51	1.25E-02
P30475	HLA class I histocompatibility antigen, B alpha chain	↑	3.60	2.66E-03
P09525	Annexin A4	↑	3.62	3.83E-02
P12931	Proto-oncogene tyrosine-protein kinase Src	↑	3.62	2.29E-04
O75891	Cytosolic 10-formyltetrahydrofolate dehydrogenase	↑	3.65	2.68E-02
P50395	Rab GDP dissociation inhibitor beta	↑	3.67	1.36E-02
Q92484	Acid sphingomyelinase-like phosphodiesterase 3a	↑	3.74	7.03E-03
A0A0A0MSA0	Laminin subunit alpha-3	↑	3.74	4.77E-02
A0A0D9SG04	Cordon-bleu WH2 repeat protein like 1	↑	3.74	1.96E-02
A0A075B6K4	Immunoglobulin lambda variable 3-10	↑	3.93	2.77E-02
A0A1W2PNV4	Actin-related protein 2/3 complex subunit 1A	↑	3.94	4.88E-02
Q9NS68	Tumor necrosis factor receptor superfamily member 19	↑	4.08	1.10E-02
Q9BXJ7	Protein amnionless	↑	4.13	2.03E-02
Q8WWY7	WAP four-disulfide core domain protein 12	↑	4.21	3.05E-02
P05186	Alkaline phosphatase, tissue-nonspecific isozyme	↑	4.21	1.33E-02
Q96A22	Uncharacterized protein C11orf52	↑	4.27	4.93E-03
Q15181	Inorganic pyrophosphatase	↑	4.35	2.72E-02
E9PL83	Pro-adrenomedullin	↑	4.39	6.36E-03
Q15848	Adiponectin	↑	4.44	2.37E-02
Q3LXA3	Triokinase/FMN cyclase	↑	4.45	2.33E-02
Q15149	Plectin	↑	4.55	1.72E-02

Q6UXN8	C-type lectin domain family 9 member A	↑	4.65	4.80E-02
Q04917	14-3-3 protein eta	↑	4.67	3.66E-02
F5H1S8	Malectin	↑	4.67	1.41E-03
Q15833	Syntaxin-binding protein 2	↑	4.73	3.36E-03
E7END7	Ras-related protein Rab-1A	↑	4.78	2.11E-02
K7EIK7	EMAP like 2	↑	4.79	2.38E-02
Q8N436	Inactive carboxypeptidase-like protein X2	↑	4.80	4.80E-02
P04279	Semenogelin-1	↑	4.86	1.63E-03
E7EMR3	Adhesion G protein-coupled receptor L3	↑	4.87	6.15E-04
Q9UHI8	A disintegrin and metalloproteinase with thrombospondin motifs 1	↑	4.89	4.37E-03
A0A075B788	Protein tyrosine phosphatase receptor type C	↑	4.90	2.91E-02
D6RHW5	Endomucin	↑	4.92	3.15E-02
A0A0B4J2C3	Translationally-controlled tumor protein	↑	4.95	4.63E-02
K7ELM9	Apolipoprotein C1	↑	5.05	2.39E-04
Q8NFY4	Semaphorin-6D	↑	5.09	3.00E-02
P14091	Cathepsin E	↑	5.14	2.63E-02
O43396	Thioredoxin-like protein 1	↑	5.17	4.49E-02
Q56A73	Spindlin-4	↑	5.19	1.11E-02
Q1EHB4	Sodium-coupled monocarboxylate transporter 2	↑	5.19	1.60E-02
P22894	Neutrophil collagenase	↑	5.19	1.99E-02
Q14142	Tripartite motif-containing protein 14	↑	5.20	2.13E-02
P21583	Kit ligand	↑	5.20	4.34E-02
Q9BY43	Charged multivesicular body protein 4a	↑	5.25	1.61E-02
B0YIW2	Apolipoprotein C-III	↑	5.27	2.25E-02
E9PGC5	protein-tyrosine-phosphatase	↑	5.29	9.03E-03
P26641	Elongation factor 1-gamma	↑	5.33	1.39E-02
J3KNP4	Semaphorin-4B	↑	5.35	4.36E-02
Q9UHG3	Prenylcysteine oxidase 1	↑	5.41	4.06E-02
H7BY57	Neurofascin	↑	5.49	1.68E-03
J3KNF4	Superoxide dismutase copper chaperone	↑	5.54	4.95E-02
F5H4M7	Transmembrane p24 trafficking protein 3	↑	5.60	4.49E-02
A0A0A0MSS8	Aldo-keto reductase family 1 member C3	↑	5.71	1.28E-02
P25786	Proteasome subunit alpha type-1	↑	5.71	1.14E-03
A0A0U1RQV3	EGF containing fibulin extracellular matrix protein 1	↑	5.79	3.16E-02
P12277	Creatine kinase B-type	↑	5.81	1.49E-02
Q8WU39	Marginal zone B- and B1-cell-specific protein	↑	5.89	7.74E-03
A0A0C4DGE4	Syntaxin 3	↑	5.92	1.72E-02
A0A087WSY5	Carboxypeptidase B2	↑	6.13	3.36E-02
P31327	Carbamoyl-phosphate synthase [ammonia], mitochondrial	↑	6.27	3.68E-02
Q9NRA1	Platelet-derived growth factor C	↑	6.32	4.69E-02
O00764	Pyridoxal kinase	↑	6.39	4.16E-02
A0A3B3IQ51	Complement factor H related 2	↑	6.53	2.01E-02

P00533	Epidermal growth factor receptor	↑	6.66	4.06E-02
A0A0A0MQV3	Kin of IRRE-like protein 2	↑	6.97	3.57E-03
Q6ZMJ2	Scavenger receptor class A member 5	↑	7.05	1.67E-02
O00401	Actin nucleation-promoting factor WASL	↑	7.12	3.17E-04
Q6H9L7	Isthmin-2	↑	7.16	3.18E-02
O60449	Lymphocyte antigen 75	↑	7.20	3.83E-03
Q86SF2	N-acetylgalactosaminyltransferase 7	↑	7.35	4.67E-03
Q8IZJ3	C3 and PZP-like alpha-2-macroglobulin domain-containing protein 8	↑	7.43	8.86E-03
B5MBX2	Transcobalamin-2	↑	7.43	4.49E-02
O00144	Frizzled-9	↑	8.31	2.02E-03
A0A2R8YE63	Epidermal growth factor receptor pathway substrate 8	↑	8.93	1.35E-02
P24298	Alanine aminotransferase 1	↑	9.03	3.68E-02
Q9BR76	Coronin-1B	↑	9.62	3.28E-02
P00742	Coagulation factor X	↑	10.39	4.09E-03
Q9HCH3	Copine-5	↑	10.69	2.73E-02
H0Y4H3	CD99 antigen-like protein 2	↑	10.74	1.19E-02
O95154	Aflatoxin B1 aldehyde reductase member 3	↑	11.67	1.11E-02
O95817	BAG family molecular chaperone regulator 3	↑	11.68	4.72E-03
Q8N8Z6	Discoidin, CUB and LCCL domain-containing protein 1	↑	12.44	2.60E-02
O60784	Target of Myb1 membrane trafficking protein	↑	12.51	1.32E-02
A5D8V6	Vacuolar protein sorting-associated protein 37C	↑	13.18	7.35E-03
P98161	Polycystin-1	↑	13.42	2.48E-02
Q9P1F3	Costars family protein ABRACL	↑	13.76	1.90E-02
P00568	Adenylate kinase isoenzyme 1	↑	15.07	1.19E-02
Q9H190	Syntenin-2	↑	21.77	9.21E-03

表 S4 宽松条件下健康组与抑郁组相比产生的差异蛋白富集到的生物学过程和信号通路(P<0.05)

BP	P-Value	Pathway	P-Value
cell adhesion	7.40E-14	Cell adhesion molecules	9.70E-07
negative regulation of fibrinolysis	5.50E-07	Lysosome	4.90E-06
complement activation, classical pathway	1.20E-06	ECM-receptor interaction	3.30E-05
axon guidance	1.30E-05	PI3K-Akt signaling pathway	7.80E-05
homophilic cell adhesion via plasma membrane adhesion molecules	2.90E-05	Focal adhesion	8.50E-05
positive regulation of B cell activation	6.50E-05	Amoebiasis	9.80E-05
leukocyte cell-cell adhesion	6.90E-05	Phagosome	1.00E-04
phagocytosis, recognition	7.00E-05	Complement and coagulation cascades	1.70E-04
proteolysis	7.80E-05	Regulation of actin cytoskeleton	2.80E-04
B cell receptor signaling pathway	1.10E-04	Proteoglycans in cancer	3.70E-04
cell migration	1.20E-04	Human papillomavirus infection	1.10E-03
regulation of cell adhesion	1.70E-04	Pathogenic Escherichia coli infection	3.30E-03
phagocytosis, engulfment	2.00E-04	Gap junction	5.40E-03
extracellular matrix organization	2.50E-04	Adherens junction	7.00E-03
antibacterial humoral response	2.90E-04	Pathways in cancer	8.20E-03
peptidyl-tyrosine phosphorylation	3.90E-04	Protein digestion and absorption	1.10E-02
calcium-dependent cell-cell adhesion via plasma membrane cell adhesion molecules	4.90E-04	Leukocyte transendothelial migration	1.80E-02
adaptive immune response	6.20E-04	Carbon metabolism	1.90E-02
positive regulation of MAP kinase activity	6.60E-04	Legionellosis	2.00E-02
positive regulation of extrinsic apoptotic signaling pathway	7.10E-04	Galactose metabolism	2.00E-02
cell-matrix adhesion	7.60E-04	Viral myocarditis	2.40E-02
female pregnancy	9.80E-04	Small cell lung cancer	2.70E-02
response to glucocorticoid	1.10E-03	AGE-RAGE signaling pathway in diabetic complications	3.60E-02
adherens junction organization	1.20E-03	Apoptosis	3.90E-02
immunoglobulin mediated immune response	1.20E-03	Bladder cancer	3.90E-02
cellular response to amino acid stimulus	1.30E-03	Rap1 signaling pathway	3.90E-02
immune response	1.50E-03	Endocytosis	4.10E-02
cell-cell adhesion	1.50E-03	NF-kappa B signaling pathway	4.20E-02
positive regulation of peptidyl-tyrosine phosphorylation	1.60E-03	Melanoma	4.30E-02
cell surface receptor signaling pathway	1.70E-03	Alzheimer disease	4.90E-02
positive regulation of protein kinase B signaling	2.00E-03	-	-
translational elongation	2.10E-03	-	-
defense response to bacterium	2.20E-03	-	-
cell adhesion mediated by integrin	2.30E-03	-	-
skeletal system development	2.50E-03	-	-
viral entry into host cell	2.80E-03	-	-
animal organ morphogenesis	3.00E-03	-	-

endocytosis	3.00E-03	-	-
basement membrane organization	3.20E-03	-	-
synapse assembly	3.30E-03	-	-
positive regulation of cell migration	3.40E-03	-	-
regulation of peptidyl-tyrosine phosphorylation	3.70E-03	-	-
positive regulation of neutrophil extravasation	3.80E-03	-	-
negative regulation of monocyte chemotaxis	3.80E-03	-	-
collagen fibril organization	3.90E-03	-	-
response to food	4.70E-03	-	-
cellular response to reactive oxygen species	4.80E-03	-	-
zymogen activation	5.20E-03	-	-
complement activation	5.20E-03	-	-
signal transduction	5.60E-03	-	-
innate immune response	6.00E-03	-	-
renal absorption	6.30E-03	-	-
heterophilic cell-cell adhesion via plasma membrane cell adhesion molecules	6.40E-03	-	-
leukocyte migration	6.50E-03	-	-
protein autoprocessing	6.50E-03	-	-
positive regulation of phosphatidylinositol 3-kinase signaling	6.60E-03	-	-
lysosome organization	6.80E-03	-	-
negative regulation of endopeptidase activity	7.20E-03	-	-
cellular response to cAMP	7.70E-03	-	-
angiogenesis	8.80E-03	-	-
carbohydrate metabolic process	1.10E-02	-	-
regulation of blood coagulation	1.10E-02	-	-
cytolysis by host of symbiont cells	1.10E-02	-	-
tissue development	1.20E-02	-	-
neuromuscular process controlling posture	1.30E-02	-	-
positive regulation of integrin-mediated signaling pathway	1.30E-02	-	-
triglyceride metabolic process	1.40E-02	-	-
cell-cell adhesion via plasma-membrane adhesion molecules	1.50E-02	-	-
negative regulation of blood coagulation	1.50E-02	-	-
positive regulation of tumor necrosis factor production	1.50E-02	-	-
positive regulation of NIK/NF-kappaB signaling	1.60E-02	-	-
central nervous system development	1.60E-02	-	-
antimicrobial humoral immune response mediated by antimicrobial peptide	1.70E-02	-	-
negative regulation of intrinsic apoptotic signaling pathway in response to DNA damage	1.70E-02	-	-

peptide metabolic process	1.70E-02	-	-
positive regulation of cell proliferation	1.80E-02	-	-
integrin-mediated signaling pathway	1.80E-02	-	-
cellular oxidant detoxification	1.90E-02	-	-
high-density lipoprotein particle remodeling	2.00E-02	-	-
regulation of cell migration	2.00E-02	-	-
cellular response to mechanical stimulus	2.00E-02	-	-
protein catabolic process	2.00E-02	-	-
positive regulation of blood pressure	2.20E-02	-	-
receptor-mediated endocytosis	2.20E-02	-	-
kidney development	2.30E-02	-	-
cell-cell junction assembly	2.50E-02	-	-
regulation of embryonic development	2.60E-02	-	-
fibrinolysis	2.70E-02	-	-
negative regulation of anoikis	2.70E-02	-	-
triglyceride catabolic process	3.00E-02	-	-
response to peptide hormone	3.10E-02	-	-
myoblast differentiation	3.30E-02	-	-
lipoprotein metabolic process	3.30E-02	-	-
establishment of endothelial barrier	3.30E-02	-	-
positive regulation of ERK1 and ERK2 cascade	3.60E-02	-	-
positive regulation of vascular smooth muscle cell proliferation	3.60E-02	-	-
positive regulation of receptor-mediated endocytosis	3.60E-02	-	-
viral budding via host ESCRT complex	3.60E-02	-	-
lysosomal lumen acidification	3.60E-02	-	-
positive regulation of smooth muscle cell migration	3.60E-02	-	-
cell morphogenesis	4.00E-02	-	-
T cell extravasation	4.10E-02	-	-
susceptibility to natural killer cell mediated cytotoxicity	4.10E-02	-	-
smooth muscle cell proliferation	4.10E-02	-	-
adhesion of symbiont to host	4.10E-02	-	-
oligopeptide transport	4.10E-02	-	-
bone regeneration	4.10E-02	-	-
blood coagulation, common pathway	4.10E-02	-	-
positive regulation of vascular associated smooth muscle cell migration	4.20E-02	-	-
negative regulation of cell migration	4.20E-02	-	-
apoptotic process	4.50E-02	-	-
cellular response to platelet-derived growth factor stimulus	4.60E-02	-	-

immune system process	4.70E-02	-	-
positive regulation of cell adhesion	4.70E-02	-	-
response to lipopolysaccharide	4.70E-02	-	-
multicellular organism development	4.80E-02	-	-

表 S5 双相患者与抑郁患者相比的差异蛋白 (FC≥1.5 或≤0.67, P<0.05)

Accession	Protein names	Trend	FC	P-Value
A0A0U1RR32	Histone H2A	↓	0.38	3.03E-02
Q53TN4	Plasma membrane ascorbate-dependent reductase CYBRD1	↓	0.48	7.17E-03
F8VNT9	CD63 molecule	↓	0.48	5.11E-03
Q9H1C7	Cysteine-rich and transmembrane domain-containing protein 1	↓	0.48	4.29E-03
P20073	Annexin A7	↓	0.54	1.13E-02
O60293	Zinc finger C3H1 domain-containing protein	↓	0.56	1.40E-02
Q9BUT1	Dehydrogenase/reductase SDR family member 6	↓	0.57	4.12E-02
P05154	Plasma serine protease inhibitor	↓	0.57	1.29E-02
Q9BXP8	Pappalysin-2	↓	0.57	3.30E-02
P16278	Beta-galactosidase	↓	0.58	4.75E-02
O43895	Xaa-Pro aminopeptidase 2	↓	0.59	3.60E-02
Q8WUM4	Programmed cell death 6-interacting protein	↓	0.59	2.27E-02
P26038	Moesin	↓	0.60	6.23E-03
Q9NZH0	G-protein coupled receptor family C group 5 member B	↓	0.60	2.27E-02
Q8IWA5	Choline transporter-like protein 2	↓	0.61	1.47E-02
A0A0C4DFY5	G protein-coupled receptor class C group 5 member C	↓	0.61	1.08E-02
P16870	Carboxypeptidase E	↓	0.63	4.24E-02
O00115	Deoxyribonuclease-2-alpha	↓	0.64	4.42E-02
O43633	Charged multivesicular body protein 2a	↓	0.65	8.83E-03
Q7LBR1	Charged multivesicular body protein 1b	↓	0.65	3.37E-02
P23284	Peptidyl-prolyl cis-trans isomerase B	↓	0.65	1.01E-03
Q9H3G5	Probable serine carboxypeptidase CPVL	↓	0.65	4.57E-02
A0A2R8Y5S7	Radixin	↓	0.66	1.26E-02
P19440	Glutathione hydrolase 1 proenzyme	↓	0.66	1.14E-02
Q08174	Protocadherin-1	↑	1.50	3.61E-03
O75594	Peptidoglycan recognition protein 1	↑	1.50	2.77E-03
A0M8Q6	Immunoglobulin lambda constant 7	↑	1.50	4.62E-03
Q24JP5	Transmembrane protein 132A	↑	1.51	3.29E-02
Q06828	Fibromodulin	↑	1.51	2.54E-02
P61981	14-3-3 protein gamma	↑	1.51	2.62E-02
A0A087WYL5	Seizure related 6 homolog like 2	↑	1.51	2.22E-02
P98172	Ephrin-B1	↑	1.51	2.65E-02
O43866	CD5 antigen-like	↑	1.52	3.30E-02
G3V3X5	Latent transforming growth factor beta binding protein 2	↑	1.52	2.02E-03
Q9UM22	Mammalian ependymin-related protein 1	↑	1.52	2.74E-02
Q9BVM4	Gamma-glutamylaminecyclotransferase	↑	1.52	4.25E-02
E5RHN3	Hepatitis A virus cellular receptor 2	↑	1.52	1.55E-02
P05362	Intercellular adhesion molecule 1	↑	1.52	4.01E-02
B1ALM4	Transmembrane protein 9	↑	1.52	4.14E-02
P98095	Fibulin-2	↑	1.52	4.52E-02
P15529	Membrane cofactor protein	↑	1.53	4.76E-02
F8VUF6	Decorin	↑	1.53	3.22E-02

P08138	Tumor necrosis factor receptor superfamily member 16	↑	1.53	1.00E-02
P18206	Vinculin	↑	1.54	9.94E-03
Q14376	UDP-glucose 4-epimerase	↑	1.55	1.31E-02
P01701	Immunoglobulin lambda variable 1-51	↑	1.55	2.85E-02
F6Q0M4	TNF receptor superfamily member 14	↑	1.55	7.69E-03
P09758	Tumor-associated calcium signal transducer 2	↑	1.55	4.97E-02
Q86V85	Integral membrane protein GPR180	↑	1.55	1.47E-02
Q02487	Desmocollin-2	↑	1.55	2.37E-02
P35754	Glutaredoxin-1	↑	1.56	1.48E-02
P36955	Pigment epithelium-derived factor	↑	1.56	4.85E-02
Q9UIB8	SLAM family member 5	↑	1.56	3.24E-03
Q14508	WAP four-disulfide core domain protein 2	↑	1.56	1.11E-02
Q9NPY3	Complement component C1q receptor	↑	1.56	4.49E-02
Q01459	Di-N-acetylchitobiase	↑	1.57	2.39E-02
P10809	60 kDa heat shock protein, mitochondrial	↑	1.57	1.73E-02
O94910	Adhesion G protein-coupled receptor L1	↑	1.57	6.58E-03
H0Y3Z8	IFNAR2-IL10RB readthrough	↑	1.58	3.70E-02
P13671	Complement component C6	↑	1.58	2.35E-02
A0A0B4J1X5	Immunoglobulin heavy variable 3-74	↑	1.58	5.25E-03
E9PMI0	Layilin	↑	1.59	1.16E-02
B4DV12	Ubiquitin B	↑	1.59	4.90E-02
B1AP13	CD55 molecule	↑	1.59	3.83E-02
A0A0C4DGH0	CD276 molecule	↑	1.59	1.33E-02
P78324	Tyrosine-protein phosphatase non-receptor type substrate 1	↑	1.59	5.56E-03
P16152	Carbonyl reductase [NADPH] 1	↑	1.59	2.30E-02
P13284	Gamma-interferon-inducible lysosomal thiol reductase	↑	1.60	1.31E-02
Q92520	Protein FAM3C	↑	1.60	1.13E-03
Q9Y646	Carboxypeptidase Q	↑	1.61	2.87E-03
K7ELL7	Glucosidase 2 subunit beta	↑	1.62	6.07E-03
P12814	Alpha-actinin-1	↑	1.62	1.82E-03
P20933	N(4)-(beta-N-acetylglucosaminyl)-L-asparaginase	↑	1.63	9.33E-03
P15121	Aldo-keto reductase family 1 member B1	↑	1.63	2.30E-02
O96009	Napsin-A	↑	1.64	4.39E-02
A0A096LP69	CD99 molecule	↑	1.64	4.84E-02
P55290	Cadherin-13	↑	1.64	3.38E-02
P06681	Complement C2	↑	1.64	1.31E-02
A0A0U1RQC5	Neurexin 3	↑	1.64	2.40E-02
P80370	Protein delta homolog 1	↑	1.65	1.07E-02
O60939	Sodium channel subunit beta-2	↑	1.66	3.81E-02
Q12864	Cadherin-17	↑	1.66	7.29E-03
O75071	EF-hand calcium-binding domain-containing protein 14	↑	1.66	1.86E-02
P0DJD8	Pepsin A-3	↑	1.66	4.87E-02
A0A2R8Y430	Glutathione synthetase	↑	1.66	2.14E-02
P0DOX8	Immunoglobulin lambda-1 light chain	↑	1.66	1.21E-02

I3L192	Basigin	↑	1.66	1.68E-02
A0A0A0MS43	Solute carrier family 10 member 3	↑	1.66	2.54E-03
P00747	Plasminogen	↑	1.67	1.47E-02
J3KSN0	Secreted and transmembrane 1	↑	1.68	1.21E-02
Q07654	Trefoil factor 3	↑	1.68	1.69E-02
Q14126	Desmoglein-2	↑	1.68	3.18E-02
Q7Z4R8	UPF0669 protein C6orf120	↑	1.68	9.72E-03
Q96J84	Kin of IRRE-like protein 1	↑	1.68	1.10E-03
P0DOX5	Immunoglobulin gamma-1 heavy chain	↑	1.69	1.39E-03
F8VVI9	Cadherin 19	↑	1.69	1.18E-02
Q6FHJ7	Secreted frizzled-related protein 4	↑	1.70	1.63E-02
P01717	Immunoglobulin lambda variable 3-25	↑	1.70	3.16E-02
P01178	Oxytocin-neurophysin 1	↑	1.70	1.95E-02
P02753	Retinol-binding protein 4	↑	1.71	7.17E-03
P10645	Chromogranin-A	↑	1.71	1.97E-02
P19961	Alpha-amylase 2B	↑	1.72	4.17E-02
E9PG71	receptor protein-tyrosine kinase	↑	1.72	3.00E-02
P02768	Albumin	↑	1.72	1.18E-02
P01834	Immunoglobulin kappa constant	↑	1.73	3.59E-02
Q16581	C3a anaphylatoxin chemotactic receptor	↑	1.73	3.25E-02
Q03403	Trefoil factor 2	↑	1.73	3.11E-03
P31997	Carcinoembryonic antigen-related cell adhesion molecule 8	↑	1.73	1.83E-02
Q02747	Guanylin	↑	1.74	4.13E-02
P11362	Fibroblast growth factor receptor 1	↑	1.74	1.00E-02
Q16610	Extracellular matrix protein 1	↑	1.75	4.59E-02
Q04721	Neurogenic locus notch homolog protein 2	↑	1.75	4.08E-03
P54826	Growth arrest-specific protein 1	↑	1.75	4.78E-02
P27797	Calreticulin	↑	1.75	2.94E-03
P26992	Ciliary neurotrophic factor receptor subunit alpha	↑	1.75	4.36E-03
Q02413	Desmoglein-1	↑	1.76	4.84E-03
O76076	CCN family member 5	↑	1.76	1.24E-02
Q68CJ9	Cyclic AMP-responsive element-binding protein 3-like protein 3	↑	1.77	1.02E-02
Q9Y5E4	Protocadherin beta-5	↑	1.77	2.81E-02
J3QLM0	CD7 molecule	↑	1.77	1.26E-03
P01210	Proenkephalin-A	↑	1.78	1.07E-02
P41222	Prostaglandin-H2 D-isomerase	↑	1.79	4.14E-02
Q99426	Tubulin-folding cofactor B	↑	1.80	1.92E-02
Q68D85	Natural cytotoxicity triggering receptor 3 ligand 1	↑	1.80	2.18E-03
E7EV71	Latent transforming growth factor beta binding protein 1	↑	1.80	3.11E-02
P61769	Beta-2-microglobulin	↑	1.81	2.19E-02
Q13308	Inactive tyrosine-protein kinase 7	↑	1.81	4.85E-04
Q16769	Glutaminyl-peptide cyclotransferase	↑	1.81	8.17E-03
Q6ZVN8	Hemojuvelin	↑	1.83	4.96E-02
Q7L266	Isoaspartyl peptidase/L-asparaginase	↑	1.83	2.78E-03

P30085	UMP-CMP kinase	↑	1.83	3.72E-03
A0A0A0MRJ7	Coagulation factor V	↑	1.83	3.51E-02
P26842	CD27 antigen	↑	1.84	2.58E-03
A0A0G2JSC0	Immunoglobulin lambda variable 5-45	↑	1.84	4.05E-02
Q92563	Testican-2	↑	1.84	4.41E-02
P22897	Macrophage mannose receptor 1	↑	1.85	2.33E-02
A0A075B6K5	Immunoglobulin lambda variable 3-9	↑	1.85	3.20E-02
B5A977	Soluble TNFR1B variant 1	↑	1.85	9.52E-03
A0A087X054	Hypoxia up-regulated protein 1	↑	1.86	2.24E-02
Q9H8L6	Multimerin-2	↑	1.86	1.33E-03
Q9BSG0	Protease-associated domain-containing protein 1	↑	1.86	1.42E-02
P98160	Basement membrane-specific heparan sulfate proteoglycan core protein	↑	1.86	9.08E-03
A6NC48	ADP-ribosyl cyclase/cyclic ADP-ribose hydrolase	↑	1.86	1.82E-03
A0A0J9YYC8	Serine protease 2	↑	1.86	2.32E-02
P31025	Lipocalin-1	↑	1.86	1.99E-02
P02749	Beta-2-glycoprotein 1	↑	1.87	9.88E-04
A0A0C4DH38	Immunoglobulin heavy variable 5-51	↑	1.87	2.85E-03
Q13291	Signaling lymphocytic activation molecule	↑	1.87	5.77E-03
Q9BRA2	Thioredoxin domain-containing protein 17	↑	1.87	9.54E-03
O75084	Frizzled-7	↑	1.88	2.69E-03
A0A0J9YX35	Immunoglobulin heavy variable 3-64D	↑	1.88	1.48E-02
Q9BQI0	Allograft inflammatory factor 1-like	↑	1.91	4.13E-02
P50591	Tumor necrosis factor ligand superfamily member 10	↑	1.91	2.38E-02
Q9UGT4	Sushi domain-containing protein 2	↑	1.91	3.31E-02
Q8N307	Mucin-20	↑	1.91	9.01E-03
Q9Y279	V-set and immunoglobulin domain-containing protein 4	↑	1.91	4.69E-02
P12830	Cadherin-1	↑	1.92	4.37E-02
P15814	Immunoglobulin lambda-like polypeptide 1	↑	1.92	8.12E-04
P14174	Macrophage migration inhibitory factor	↑	1.92	1.26E-02
B8ZZ73	Interleukin 1 receptor type 1	↑	1.93	5.50E-04
O94919	Endonuclease domain-containing 1 protein	↑	1.93	1.27E-02
Q8TBP5	Membrane protein FAM174A	↑	1.93	4.99E-02
Q9UHR4	Brain-specific angiogenesis inhibitor 1-associated protein 2-like protein 1	↑	1.94	8.90E-03
A0A0A0MS15	Immunoglobulin heavy variable 3-49	↑	1.94	8.76E-04
P31151	Protein S100-A7	↑	1.95	1.90E-02
O60279	Sushi domain-containing protein 5	↑	1.96	1.40E-02
A0A075B6R2	Immunoglobulin heavy variable 4-4	↑	1.96	1.57E-03
J3KPQ0	Fibroblast growth factor receptor	↑	1.97	8.14E-03
P23083	Immunoglobulin heavy variable 1-2	↑	1.98	6.43E-04
J3QRS3	Myosin light chain 12A	↑	1.98	6.59E-04
Q92626	Peroxidasin homolog	↑	1.98	4.88E-02
Q92496	Complement factor H-related protein 4	↑	1.99	6.92E-03

P02760	Protein AMBP	↑	2.01	1.16E-02
Q14315	Filamin-C	↑	2.01	6.51E-03
Q14118	Dystroglycan 1	↑	2.01	2.27E-02
A0A0B4J2B5	Immunoglobulin heavy variable 3/OR16-9	↑	2.01	9.88E-03
O75368	Adapter SH3BGRL	↑	2.02	3.06E-03
O00187	Mannan-binding lectin serine protease 2	↑	2.03	2.99E-02
A0A0J9YY99	Ig-like domain-containing protein	↑	2.03	6.26E-04
A0A087X0H5	Growth hormone receptor	↑	2.03	4.41E-03
P06396	Gelsolin	↑	2.04	3.25E-02
A0A0A0MR25	Fibroblast growth factor receptor	↑	2.04	6.12E-03
Q9UFM8	Neuroplastin	↑	2.04	2.87E-02
Q9H461	Frizzled-8	↑	2.05	1.02E-04
P48745	CCN family member 3	↑	2.07	3.41E-03
P55000	Secreted Ly-6/uPAR-related protein 1	↑	2.08	1.10E-04
Q9H1E1	Ribonuclease 7	↑	2.08	1.81E-02
Q9GZM7	Tubulointerstitial nephritis antigen-like	↑	2.08	3.43E-04
P02765	Alpha-2-HS-glycoprotein	↑	2.08	8.41E-03
P32942	Intercellular adhesion molecule 3	↑	2.09	9.22E-05
E7EMR3	Adhesion G protein-coupled receptor L3	↑	2.09	1.88E-02
P00918	Carbonic anhydrase 2	↑	2.11	5.39E-03
P81605	Dermcidin	↑	2.12	5.81E-03
P02452	Collagen alpha-1	↑	2.13	2.48E-03
H7C3P2	Collagen type XXVIII alpha 1 chain	↑	2.13	2.36E-03
Q6ZNA5	Ferric-chelate reductase 1	↑	2.14	3.44E-02
I3L0L6	E3 ubiquitin-protein ligase RNF167	↑	2.15	2.90E-02
Q15375	Ephrin type-A receptor 7	↑	2.16	5.28E-04
Q13790	Apolipoprotein F	↑	2.19	1.34E-03
K3W4U1	Fc epsilon receptor II	↑	2.20	1.11E-03
P04196	Histidine-rich glycoprotein	↑	2.21	6.77E-03
P07437	Tubulin beta chain	↑	2.21	8.04E-03
O43570	Carbonic anhydrase 12	↑	2.22	1.10E-05
Q9ULV1	Frizzled-4	↑	2.23	1.56E-02
Q15828	Cystatin-M	↑	2.23	3.37E-02
Q5T123	SH3 domain-binding glutamic acid-rich-like protein 3	↑	2.25	1.46E-02
O94760	Dimethylarginine dimethylaminohydrolase 1	↑	2.25	2.80E-03
O00401	Actin nucleation-promoting factor WASL	↑	2.27	3.31E-02
Q96IU4	Putative protein-lysine deacylase ABHD14B	↑	2.27	1.07E-04
P29692	Elongation factor 1-delta	↑	2.28	3.18E-03
P83110	Serine protease HTRA3	↑	2.30	7.00E-04
A0A087WX80	Laminin subunit alpha 2	↑	2.30	2.40E-03
P01714	Immunoglobulin lambda variable 3-19	↑	2.31	1.88E-02
Q5KU26	Collectin-12	↑	2.31	4.58E-02
P0DOY3	Immunoglobulin lambda constant 3	↑	2.31	1.52E-02
F6SYF8	Dickkopf WNT signaling pathway inhibitor 3	↑	2.32	1.57E-03

P13647	Keratin, type II cytoskeletal 5	↑	2.33	3.15E-02
Q6PI73	Leukocyte immunoglobulin-like receptor subfamily A member 6	↑	2.33	2.48E-02
Q99983	Osteomodulin	↑	2.34	3.81E-02
P22304	Iduronate 2-sulfatase	↑	2.35	1.45E-02
P10109	Adrenodoxin, mitochondrial	↑	2.35	1.48E-02
Q9Y5Z4	Heme-binding protein 2	↑	2.37	3.18E-02
O95388	CCN family member 4	↑	2.38	1.59E-03
Q96S96	Phosphatidylethanolamine-binding protein 4	↑	2.40	1.35E-02
O95971	CD160 antigen	↑	2.40	3.18E-03
P04430	Immunoglobulin kappa variable 1-16	↑	2.41	3.33E-02
O95841	Angiopoietin-related protein 1	↑	2.41	2.50E-03
P29401	Transketolase	↑	2.44	2.98E-02
P19823	Inter-alpha-trypsin inhibitor heavy chain H2	↑	2.45	2.81E-02
P55259	Pancreatic secretory granule membrane major glycoprotein GP2	↑	2.46	1.18E-02
A0A0C4DH43	Immunoglobulin heavy variable 2-70D	↑	2.51	1.65E-03
Q8NFT8	Delta and Notch-like epidermal growth factor-related receptor	↑	2.52	8.38E-04
Q9NY37	Acid-sensing ion channel 5	↑	2.53	6.05E-03
O15145	Actin-related protein 2/3 complex subunit 3	↑	2.54	1.20E-02
P16989	Y-box-binding protein 3	↑	2.54	7.16E-03
A0A3B3IRL2	Cellular repressor of E1A stimulated genes 1	↑	2.55	1.81E-02
A0A286YFJ8	Immunoglobulin heavy constant gamma 4	↑	2.55	1.72E-02
P04155	Trefoil factor 1	↑	2.57	9.53E-03
Q16348	Solute carrier family 15 member 2	↑	2.58	4.87E-02
F8W1A4	Adenylate kinase 2, mitochondrial	↑	2.59	2.60E-02
Q92765	Secreted frizzled-related protein 3	↑	2.59	5.62E-03
Q9HB75	p53-induced death domain-containing protein 1	↑	2.60	1.47E-03
P00491	Purine nucleoside phosphorylase	↑	2.61	4.26E-02
P32320	Cytidine deaminase	↑	2.62	2.22E-02
Q9H741	SREBP regulating gene protein	↑	2.65	2.14E-02
B1AH90	Signal peptide, CUB domain and EGF like domain containing 1	↑	2.67	2.19E-02
P11766	Alcohol dehydrogenase class-3	↑	2.69	1.71E-04
P32004	Neural cell adhesion molecule L1	↑	2.70	8.43E-03
P01031	Complement C5	↑	2.71	4.92E-02
O43852	Calumenin	↑	2.72	2.52E-03
O94985	Calsyntenin-1	↑	2.73	9.80E-03
Q9UKY0	Prion-like protein doppel	↑	2.74	7.99E-03
P30046	D-dopachrome decarboxylase	↑	2.75	1.76E-02
Q96A22	Uncharacterized protein C11orf52	↑	2.76	1.90E-02
P36941	Tumor necrosis factor receptor superfamily member 3	↑	2.77	4.47E-02
P04179	Superoxide dismutase [Mn], mitochondrial	↑	2.79	4.54E-02
O75487	Glypican-4	↑	2.79	2.36E-02
Q9Y6U3	Scinderin	↑	2.81	9.36E-03
P13489	Ribonuclease inhibitor	↑	2.83	2.03E-02
P30044	Peroxiredoxin-5, mitochondrial	↑	2.86	5.29E-03

Q16661	Guanylate cyclase activator 2B	↑	2.89	9.09E-03
Q96I82	Kazal-type serine protease inhibitor domain-containing protein 1	↑	2.90	4.99E-03
P13861	cAMP-dependent protein kinase type II-alpha regulatory subunit	↑	2.91	3.77E-02
F5H1S8	Malectin	↑	2.91	6.11E-03
Q15833	Syntaxin-binding protein 2	↑	2.94	1.32E-02
P30475	HLA class I histocompatibility antigen, B alpha chain	↑	2.95	2.11E-03
E9PL83	Pro-adrenomedullin	↑	2.99	1.84E-02
O95633	Follistatin-related protein 3	↑	3.01	1.81E-02
A0A0C4DH72	Immunoglobulin kappa variable 1-6	↑	3.03	2.39E-03
P25391	Laminin subunit alpha-1	↑	3.04	5.06E-03
P18669	Phosphoglycerate mutase 1	↑	3.11	3.15E-02
Q9Y281	Cofilin-2	↑	3.11	2.29E-02
P28066	Proteasome subunit alpha type-5	↑	3.11	3.40E-02
Q9UJ72	Annexin A10	↑	3.15	7.77E-03
P05556	Integrin beta-1	↑	3.17	2.14E-04
C9JM33	Interferon alpha and beta receptor subunit 2	↑	3.21	1.55E-02
K7ELM9	Apolipoprotein C1	↑	3.22	1.24E-03
A0A1B0GTG2	Aldehyde dehydrogenase 7 family member A1	↑	3.27	1.09E-02
P27348	14-3-3 protein theta	↑	3.28	5.50E-03
P17655	Calpain-2 catalytic subunit	↑	3.30	2.52E-04
Q5VY43	Platelet endothelial aggregation receptor 1	↑	3.32	4.49E-02
Q9H0E2	Toll-interacting protein	↑	3.37	3.77E-02
P05186	Alkaline phosphatase, tissue-nonspecific isozyme	↑	3.40	2.10E-02
Q9BY89	Uncharacterized protein KIAA1671	↑	3.41	1.80E-02
O00144	Frizzled-9	↑	3.43	1.07E-02
O95980	Reversion-inducing cysteine-rich protein with Kazal motifs	↑	3.44	6.50E-03
A0A0C4DGB5	Calpastatin	↑	3.48	2.72E-02
P00738	Haptoglobin	↑	3.57	4.67E-02
P80748	Immunoglobulin lambda variable 3-21	↑	3.59	3.92E-02
G5E9G7	Neurexin 2	↑	3.61	7.17E-05
P00748	Coagulation factor XII	↑	3.63	2.10E-02
P12931	Proto-oncogene tyrosine-protein kinase Src	↑	3.66	6.34E-05
P22692	Insulin-like growth factor-binding protein 4	↑	3.68	4.02E-02
Q14142	Tripartite motif-containing protein 14	↑	3.68	3.87E-02
P28072	Proteasome subunit beta type-6	↑	3.70	2.00E-02
G3V4P8	Glia maturation factor beta	↑	3.71	4.55E-02
E7EX17	Eukaryotic translation initiation factor 4B	↑	3.73	4.97E-02
Q9UJ99	Cadherin-22	↑	3.73	1.18E-02
O75891	Cytosolic 10-formyltetrahydrofolate dehydrogenase	↑	3.74	2.44E-02
Q5T2W1	Na(+)/H(+) exchange regulatory cofactor NHE-RF3	↑	3.78	1.38E-02
D6RHW5	Endomucin	↑	3.79	4.55E-02
Q3LXA3	Triokinase/FMN cyclase	↑	3.82	3.39E-02
P20774	Mimecan	↑	3.83	3.33E-02
Q92484	Acid sphingomyelinase-like phosphodiesterase 3a	↑	3.85	3.90E-03

A0A0A0MSA0	Laminin subunit alpha-3	↑	3.90	4.37E-02
O95817	BAG family molecular chaperone regulator 3	↑	3.91	3.39E-02
Q7Z794	Keratin, type II cytoskeletal 1b	↑	3.93	2.02E-03
A0A0A0MSS8	Aldo-keto reductase family 1 member C3	↑	3.95	2.30E-02
Q8IW52	SLIT and NTRK-like protein 4	↑	3.95	4.75E-02
O95171	Sciellin	↑	3.98	3.82E-02
Q8WWA0	Intelectin-1	↑	4.21	1.30E-02
A0A0C4DGE4	Syntaxin 3	↑	4.25	2.37E-02
Q8N474	Secreted frizzled-related protein 1	↑	4.25	3.63E-02
P02042	Hemoglobin subunit delta	↑	4.27	6.34E-03
Q8WWY7	WAP four-disulfide core domain protein 12	↑	4.32	2.58E-02
P09486	Secreted protein acidic and rich in cysteine	↑	4.32	3.80E-02
Q14050	Collagen alpha-3	↑	4.35	2.01E-02
P25788	Proteasome subunit alpha type-3	↑	4.39	4.12E-02
P35579	Myosin-9	↑	4.48	2.73E-02
P29992	Guanine nucleotide-binding protein subunit alpha-11	↑	4.53	2.02E-02
P05026	Sodium/potassium-transporting ATPase subunit beta-1	↑	4.54	4.45E-03
P00740	Coagulation factor IX	↑	4.55	2.15E-02
A8MVW5	HEPACAM family member 2	↑	4.57	4.69E-02
A8K878	cDNA FLJ77177, highly similar to Homo sapiens arginine-rich, mutated in early stage tumors	↑	4.59	6.41E-03
H3BTI0	Cysteine rich secretory protein LCCL domain containing 2	↑	4.60	2.81E-02
A0A1W2PNV4	Actin-related protein 2/3 complex subunit 1A	↑	4.61	3.35E-02
Q13103	Secreted phosphoprotein 24	↑	4.63	2.33E-02
P63096	Guanine nucleotide-binding protein G	↑	4.68	3.84E-02
P00390	Glutathione reductase, mitochondrial	↑	4.68	3.76E-02
Q8WWZ8	Oncoprotein-induced transcript 3 protein	↑	4.68	4.86E-02
Q9BY43	Charged multivesicular body protein 4a	↑	4.68	1.94E-02
P52961	GPI-linked NAD	↑	4.71	3.65E-03
P05023	Sodium/potassium-transporting ATPase subunit alpha-1	↑	4.73	4.20E-02
A0A0C4DH07	Latent transforming growth factor beta binding protein 4	↑	4.76	1.18E-03
Q14697	Neutral alpha-glucosidase AB	↑	4.93	4.60E-02
Q8WWQ8	Stabilin-2	↑	4.95	1.99E-02
A0A0D9SG04	Cordon-bleu WH2 repeat protein like 1	↑	5.01	9.28E-03
P36543	V-type proton ATPase subunit E 1	↑	5.05	4.18E-02
P26641	Elongation factor 1-gamma	↑	5.05	1.46E-02
P37837	Transaldolase	↑	5.13	3.57E-02
P21399	Cytoplasmic aconitate hydratase	↑	5.15	4.07E-02
A0A075B6K4	Immunoglobulin lambda variable 3-10	↑	5.20	1.70E-02
Q9BTY2	Plasma alpha-L-fucosidase	↑	5.20	4.69E-02
Q99584	Protein S100-A13	↑	5.23	3.80E-02
Q9UHI8	A disintegrin and metalloproteinase with thrombospondin motifs 1	↑	5.30	3.33E-03
Q86UN2	Reticulon-4 receptor-like 1	↑	5.40	1.69E-02
P06858	Lipoprotein lipase	↑	5.40	1.06E-03

Q9NZ08	Endoplasmic reticulum aminopeptidase 1	↑	5.42	9.08E-03
P50502	Hsc70-interacting protein	↑	5.43	2.60E-02
Q9P1F3	Costars family protein ABRACL	↑	5.47	4.36E-02
Q10471	Polypeptide N-acetylgalactosaminyltransferase 2	↑	5.48	4.89E-02
P07357	Complement component C8 alpha chain	↑	5.48	9.60E-03
Q9UGB7	Inositol oxygenase	↑	5.52	4.03E-02
P31327	Carbamoyl-phosphate synthase [ammonia], mitochondrial	↑	5.52	4.10E-02
B1AK87	F-actin-capping protein subunit beta	↑	5.56	3.08E-02
A6NKB8	Arginyl aminopeptidase	↑	5.57	1.34E-02
O60449	Lymphocyte antigen 75	↑	5.57	6.72E-03
P46940	Ras GTPase-activating-like protein IQGAP1	↑	5.58	4.44E-02
P06748	Nucleophosmin	↑	5.62	3.73E-02
P48740	Mannan-binding lectin serine protease 1	↑	5.73	4.87E-02
P68036	Ubiquitin-conjugating enzyme E2 L3	↑	5.73	4.69E-02
Q9BQR3	Serine protease 27	↑	5.73	3.55E-02
Q01518	Adenylyl cyclase-associated protein 1	↑	5.74	4.99E-02
A0A0J9YWL0	Crystallin beta-gamma domain containing 1	↑	5.75	1.75E-02
P24752	Acetyl-CoA acetyltransferase, mitochondrial	↑	5.78	2.50E-02
Q15848	Adiponectin	↑	5.80	9.38E-03
Q86XT2	Vacuolar protein sorting-associated protein 37D	↑	5.87	5.40E-03
P98161	Polycystin-1	↑	5.96	4.42E-02
P50395	Rab GDP dissociation inhibitor beta	↑	5.96	2.79E-03
P31371	Fibroblast growth factor 9	↑	5.96	2.89E-02
A0A024R571	EH domain containing 1	↑	6.06	6.49E-03
Q14240	Eukaryotic initiation factor 4A-II	↑	6.07	1.24E-02
O00764	Pyridoxal kinase	↑	6.09	4.44E-02
P24666	Low molecular weight phosphotyrosine protein phosphatase	↑	6.14	4.84E-02
Q9H9H4	Vacuolar protein sorting-associated protein 37B	↑	6.16	4.15E-02
P61978	Heterogeneous nuclear ribonucleoprotein K	↑	6.16	2.48E-02
A0A0G2JLS4	Leukocyte immunoglobulin-like receptor subfamily B member 1	↑	6.21	9.97E-03
P55072	Transitional endoplasmic reticulum ATPase	↑	6.21	2.01E-02
Q93099	Homogentisate 1,2-dioxygenase	↑	6.24	4.04E-02
A0A0C4DFN5	Chromosome 10 open reading frame 61	↑	6.26	4.54E-02
P22894	Neutrophil collagenase	↑	6.29	1.53E-02
Q9H223	EH domain-containing protein 4	↑	6.37	3.13E-02
Q9Y5H8	Protocadherin alpha-3	↑	6.47	4.48E-02
P01817	Immunoglobulin heavy variable 2-5	↑	6.49	4.51E-02
G3V180	Dipeptidyl peptidase 3	↑	6.53	2.02E-02
Q86VZ4	Low-density lipoprotein receptor-related protein 11	↑	6.58	2.09E-02
P22314	Ubiquitin-like modifier-activating enzyme 1	↑	6.59	3.05E-02
Q9NRA1	Platelet-derived growth factor C	↑	6.59	4.42E-02
Q6UXN8	C-type lectin domain family 9 member A	↑	6.72	2.36E-02
A0A3B3IQ51	Complement factor H related 2	↑	6.76	1.96E-02
Q9NP85	Podocin	↑	6.78	2.12E-02

B5MBX2	Transcobalamin-2	↑	6.81	4.76E-02
P62070	Ras-related protein R-Ras2	↑	6.88	3.30E-02
O75354	Ectonucleoside triphosphate diphosphohydrolase 6	↑	6.94	3.80E-02
H3BMA1	Mesothelin	↑	6.97	2.77E-03
A0A087WSY5	Carboxypeptidase B2	↑	7.12	2.93E-02
Q9UHY7	Enolase-phosphatase E1	↑	7.13	3.08E-02
Q15181	Inorganic pyrophosphatase	↑	7.17	8.95E-03
Q9Y5K6	CD2-associated protein	↑	7.18	2.91E-02
O00461	Golgi integral membrane protein 4	↑	7.21	1.74E-02
P61020	Ras-related protein Rab-5B	↑	7.26	1.33E-02
Q92890	Ubiquitin recognition factor in ER-associated degradation protein 1	↑	7.28	4.85E-02
P31150	Rab GDP dissociation inhibitor alpha	↑	7.31	2.70E-02
Q13867	Bleomycin hydrolase	↑	7.39	1.67E-02
Q12765	Secernin-1	↑	7.41	1.46E-02
P40197	Platelet glycoprotein V	↑	7.45	7.87E-03
Q9UFP1	Golgi-associated kinase 1A	↑	7.46	2.78E-02
M0QYN0	Myeloid derived growth factor	↑	7.49	2.18E-03
P28332	Alcohol dehydrogenase 6	↑	7.51	3.16E-02
P21964	Catechol O-methyltransferase	↑	7.53	1.92E-02
P21583	Kit ligand	↑	7.54	2.35E-02
E9PGC5	protein-tyrosine-phosphatase	↑	7.56	2.58E-03
Q6ZMJ2	Scavenger receptor class A member 5	↑	7.59	1.55E-02
Q86TD4	Sarcalumenin	↑	7.65	4.96E-02
Q96KN2	Beta-Ala-His dipeptidase	↑	7.71	1.85E-02
P00742	Coagulation factor X	↑	7.82	5.44E-03
A0A075B788	Protein tyrosine phosphatase receptor type C	↑	7.89	1.08E-02
A0A0C4DGN2	Sex hormone-binding globulin	↑	7.89	2.79E-02
F5H4M7	Transmembrane p24 trafficking protein 3	↑	7.95	3.08E-02
B5MCA4	Epithelial cell adhesion molecule	↑	8.03	3.75E-02
C9J0J7	Profilin	↑	8.07	2.19E-02
Q99795	Cell surface A33 antigen	↑	8.14	5.63E-03
B7ZM79	PCDH9 protein	↑	8.22	2.08E-02
P00533	Epidermal growth factor receptor	↑	8.22	3.40E-02
Q14353	Guanidinoacetate N-methyltransferase	↑	8.23	5.25E-03
Q5VT99	Leucine-rich repeat-containing protein 38	↑	8.27	2.86E-02
P00492	Hypoxanthine-guanine phosphoribosyltransferase	↑	8.28	4.73E-03
P07384	Calpain-1 catalytic subunit	↑	8.44	2.15E-02
O43396	Thioredoxin-like protein 1	↑	8.50	2.21E-02
P09525	Annexin A4	↑	8.55	4.63E-03
P40227	T-complex protein 1 subunit zeta	↑	8.58	1.79E-02
B0YIW2	Apolipoprotein C-III	↑	8.60	9.29E-03
Q15366	Poly(rC)-binding protein 2	↑	8.73	1.24E-02
Q6H9L7	Isthmin-2	↑	8.78	2.75E-02
P06576	ATP synthase subunit beta, mitochondrial	↑	8.84	1.67E-02

Q6P4A8	Phospholipase B-like 1	↑	8.89	7.76E-03
B8ZZ19	Parvalbumin	↑	9.06	4.36E-02
A0A0U1RQV3	EGF containing fibulin extracellular matrix protein 1	↑	9.07	2.09E-02
D6RAF8	Heterogeneous nuclear ribonucleoprotein D	↑	9.12	4.32E-02
P31948	Stress-induced-phosphoprotein 1	↑	9.16	1.17E-02
Q9BR76	Coronin-1B	↑	9.18	3.36E-02
Q9UJJ9	N-acetylglucosamine-1-phosphotransferase subunit gamma	↑	9.68	2.00E-02
Q9HCH3	Copine-5	↑	9.70	2.87E-02
Q9UN75	Protocadherin alpha-12	↑	9.73	3.30E-02
P32189	Glycerol kinase	↑	10.02	1.33E-02
P29373	Cellular retinoic acid-binding protein 2	↑	10.22	4.12E-03
Q96BW5	Phosphotriesterase-related protein	↑	10.85	2.76E-03
F8WCF6	Actin-related protein 2/3 complex subunit 4	↑	10.87	2.82E-02
P37235	Hippocalcin-like protein 1	↑	10.94	2.58E-02
G3XAF7	Brain enriched myelin associated protein 1	↑	10.96	3.37E-02
A0A096LPE2	SAA2-SAA4 readthrough	↑	10.97	3.60E-03
Q15149	Plectin	↑	11.07	2.35E-03
C9JBI3	Phosphoserine phosphatase	↑	11.20	1.57E-02
Q9NYQ8	Protocadherin Fat 2	↑	11.27	3.17E-02
O60784	Target of Myb1 membrane trafficking protein	↑	11.30	1.39E-02
E9PIT4	Transmembrane protein 25	↑	11.41	3.05E-02
P24298	Alanine aminotransferase 1	↑	11.45	3.25E-02
Q9UJU6	Drebrin-like protein	↑	11.66	3.69E-02
Q6P1N0	Coiled-coil and C2 domain-containing protein 1A	↑	11.67	4.97E-02
P54652	Heat shock-related 70 kDa protein 2	↑	11.70	1.12E-02
A6NFX8	Nudix hydrolase 5	↑	11.92	2.30E-02
P18428	Lipopolysaccharide-binding protein	↑	12.15	4.31E-02
Q9BW04	Specifically androgen-regulated gene protein	↑	12.15	4.45E-02
O95154	Aflatoxin B1 aldehyde reductase member 3	↑	12.23	1.07E-02
P51149	Ras-related protein Rab-7a	↑	12.62	5.25E-03
P17405	Sphingomyelin phosphodiesterase	↑	12.96	2.45E-02
Q8N8Z6	Discoidin, CUB and LCCL domain-containing protein 1	↑	13.47	2.51E-02
Q9BXJ7	Protein amnionless	↑	13.84	1.06E-03
O14732	Inositol monophosphatase 2	↑	14.05	3.00E-02
Q09328	Alpha-1,6-mannosylglycoprotein 6-beta-N-acetylglucosaminyltransferase A	↑	14.27	7.63E-03
C9JL73	Vacuolar proton pump subunit B	↑	14.30	4.80E-02
Q04917	14-3-3 protein eta	↑	14.34	1.07E-02
B4DUR8	T-complex protein 1 subunit gamma	↑	14.64	3.46E-02
Q9Y490	Talin-1	↑	14.73	8.81E-03
Q96HC4	PDZ and LIM domain protein 5	↑	14.78	1.41E-02
P16562	Cysteine-rich secretory protein 2	↑	15.01	6.75E-03
A0A0B4J2C3	Translationally-controlled tumor protein	↑	15.06	1.39E-02
O75264	Small integral membrane protein 24	↑	15.84	1.16E-02

H0Y4H3	CD99 antigen-like protein 2	↑	16.01	9.45E-03
A5D8V6	Vacuolar protein sorting-associated protein 37C	↑	16.07	6.63E-03
Q9Y6X5	Bis(5'-adenosyl)-triphosphatase ENPP4	↑	16.22	8.25E-03
P28838	Cytosol aminopeptidase	↑	16.30	2.70E-02
B7ZAR1	T-complex protein 1 subunit epsilon	↑	16.74	2.19E-02
Q9HBJ8	Collectrin	↑	17.23	1.28E-02
O14737	Programmed cell death protein 5	↑	17.53	2.22E-02
Q9BUP0	EF-hand domain-containing protein D1	↑	17.57	1.59E-02
P09382	Galectin-1	↑	17.68	2.60E-02
O00253	Agouti-related protein	↑	17.72	1.93E-02
P04424	Argininosuccinate lyase	↑	17.99	1.66E-02
E7END6	Vitamin K-dependent protein C	↑	18.30	1.25E-02
O15144	Actin-related protein 2/3 complex subunit 2	↑	18.60	2.32E-02
P28908	Tumor necrosis factor receptor superfamily member 8	↑	18.86	3.78E-02
P49641	Alpha-mannosidase 2x	↑	19.83	3.50E-02
E7END7	Ras-related protein Rab-1A	↑	20.71	2.39E-03
Q92597	Protein NDRG1	↑	21.13	1.40E-02
P00568	Adenylate kinase isoenzyme 1	↑	21.51	1.04E-02
Q9H190	Syntenin-2	↑	21.59	9.22E-03
H7BY57	Neurofascin	↑	22.82	4.66E-05
K7EIK7	EMAP like 2	↑	24.28	2.87E-03
P45974	Ubiquitin carboxyl-terminal hydrolase 5	↑	27.83	1.17E-02

表 S6 抑郁患者与双相患者相比的差异蛋白 (FC≥2 或≤0.5, P<0.01)

Accession	Protein names	Trend	FC	P-Value
Q53TN4	Plasma membrane ascorbate-dependent reductase CYBRD1	↓	0.48	7.17E-03
F8VNT9	CD63 molecule	↓	0.48	5.11E-03
Q9H1C7	Cysteine-rich and transmembrane domain-containing protein 1	↓	0.48	4.29E-03
Q14315	Filamin-C	↑	2.01	6.51E-03
A0A0B4J2B5	Immunoglobulin heavy variable 3/OR16-9	↑	2.01	9.88E-03
O75368	Adapter SH3BGRL	↑	2.02	3.06E-03
A0A0J9YY99	Ig-like domain-containing protein	↑	2.03	6.26E-04
A0A087X0H5	Growth hormone receptor	↑	2.03	4.41E-03
A0A0A0MR25	Fibroblast growth factor receptor	↑	2.04	6.12E-03
Q9H461	Frizzled-8	↑	2.05	1.02E-04
P48745	CCN family member 3	↑	2.07	3.41E-03
P55000	Secreted Ly-6/uPAR-related protein 1	↑	2.08	1.10E-04
Q9GZM7	Tubulointerstitial nephritis antigen-like	↑	2.08	3.43E-04
P02765	Alpha-2-HS-glycoprotein	↑	2.08	8.41E-03
P32942	Intercellular adhesion molecule 3	↑	2.09	9.22E-05
P00918	Carbonic anhydrase 2	↑	2.11	5.39E-03
P81605	Dermcidin	↑	2.12	5.81E-03
P02452	Collagen alpha-1	↑	2.13	2.48E-03
H7C3P2	Collagen type XXVIII alpha 1 chain	↑	2.13	2.36E-03
Q15375	Ephrin type-A receptor 7	↑	2.16	5.28E-04
Q13790	Apolipoprotein F	↑	2.19	1.34E-03
K3W4U1	Fc epsilon receptor II	↑	2.20	1.11E-03
P04196	Histidine-rich glycoprotein	↑	2.21	6.77E-03
P07437	Tubulin beta chain	↑	2.21	8.04E-03
O43570	Carbonic anhydrase 12	↑	2.22	1.10E-05
O94760	N(G)-dimethylarginine dimethylaminohydrolase 1	↑	2.25	2.80E-03
Q96IU4	Putative protein-lysine deacylase ABHD14B	↑	2.27	1.07E-04
P29692	Elongation factor 1-delta	↑	2.28	3.18E-03
P83110	Serine protease HTRA3	↑	2.30	7.00E-04
A0A087WX80	Laminin subunit alpha 2	↑	2.30	2.40E-03
F6SYF8	Dickkopf WNT signaling pathway inhibitor 3	↑	2.32	1.57E-03
O95388	CCN family member 4	↑	2.38	1.59E-03
O95971	CD160 antigen	↑	2.40	3.18E-03
O95841	Angiopoietin-related protein 1	↑	2.41	2.50E-03
A0A0C4DH43	Immunoglobulin heavy variable 2-70D	↑	2.51	1.65E-03
Q8NFT8	Delta and Notch-like epidermal growth factor-related receptor	↑	2.52	8.38E-04
Q9NY37	Acid-sensing ion channel 5	↑	2.53	6.05E-03
P16989	Y-box-binding protein 3	↑	2.54	7.16E-03
P04155	Trefoil factor 1	↑	2.57	9.53E-03
Q92765	Secreted frizzled-related protein 3	↑	2.59	5.62E-03
Q9HB75	p53-induced death domain-containing protein 1	↑	2.60	1.47E-03
P11766	Alcohol dehydrogenase class-3	↑	2.69	1.71E-04

P32004	Neural cell adhesion molecule L1	↑	2.70	8.43E-03
O43852	Calumenin	↑	2.72	2.52E-03
O94985	Calsyntenin-1	↑	2.73	9.80E-03
Q9UKY0	Prion-like protein doppel	↑	2.74	7.99E-03
Q9Y6U3	Scinderin	↑	2.81	9.36E-03
P30044	Peroxiredoxin-5, mitochondrial	↑	2.86	5.29E-03
Q16661	Guanylate cyclase activator 2B [Cleaved into: Guanylate cyclase C-activating peptide 2	↑	2.89	9.09E-03
Q96I82	Kazal-type serine protease inhibitor domain-containing protein 1	↑	2.90	4.99E-03
F5H1S8	Malectin	↑	2.91	6.11E-03
P30475	HLA class I histocompatibility antigen, B alpha chain	↑	2.95	2.11E-03
A0A0C4DH72	Immunoglobulin kappa variable 1-6	↑	3.03	2.39E-03
P25391	Laminin subunit alpha-1	↑	3.04	5.06E-03
Q9UJ72	Annexin A10	↑	3.15	7.77E-03
P05556	Integrin beta-1	↑	3.17	2.14E-04
K7ELM9	Apolipoprotein C1	↑	3.22	1.24E-03
P27348	14-3-3 protein theta	↑	3.28	5.50E-03
P17655	Calpain-2 catalytic subunit	↑	3.30	2.52E-04
O95980	Reversion-inducing cysteine-rich protein with Kazal motifs	↑	3.44	6.50E-03
G5E9G7	Neurexin 2	↑	3.61	7.17E-05
P12931	Proto-oncogene tyrosine-protein kinase Src	↑	3.66	6.34E-05
Q92484	Acid sphingomyelinase-like phosphodiesterase 3a	↑	3.85	3.90E-03
Q7Z794	Keratin, type II cytoskeletal 1b	↑	3.93	2.02E-03
P02042	Hemoglobin subunit delta	↑	4.27	6.34E-03
P05026	Sodium/potassium-transporting ATPase subunit beta-1	↑	4.54	4.45E-03
A8K878	cDNA FLJ77177, highly similar to Homo sapiens arginine-rich, mutated in early stage tumors	↑	4.59	6.41E-03
P52961	GPI-linked NAD	↑	4.71	3.65E-03
A0A0C4DH07	Latent transforming growth factor beta binding protein 4	↑	4.76	1.18E-03
A0A0D9SG04	Cordon-bleu WH2 repeat protein like 1	↑	5.01	9.28E-03
Q9UHI8	A disintegrin and metalloproteinase with thrombospondin motifs 1	↑	5.30	3.33E-03
P06858	Lipoprotein lipase	↑	5.40	1.06E-03
Q9NZ08	Endoplasmic reticulum aminopeptidase 1	↑	5.42	9.08E-03
P07357	Complement component C8 alpha chain	↑	5.48	9.60E-03
O60449	Lymphocyte antigen 75	↑	5.57	6.72E-03
Q15848	Adiponectin	↑	5.80	9.38E-03
Q86XT2	Vacuolar protein sorting-associated protein 37D	↑	5.87	5.40E-03
P50395	Rab GDP dissociation inhibitor beta	↑	5.96	2.79E-03
A0A024R571	EH domain containing 1	↑	6.06	6.49E-03
A0A0G2JLS4	Leukocyte immunoglobulin-like receptor subfamily B member 1	↑	6.21	9.97E-03
H3BMA1	Mesothelin	↑	6.97	2.77E-03
Q15181	Inorganic pyrophosphatase	↑	7.17	8.95E-03
P40197	Platelet glycoprotein V	↑	7.45	7.87E-03
M0QYN0	Myeloid derived growth factor	↑	7.49	2.18E-03

E9PGC5	protein-tyrosine-phosphatase	↑	7.56	2.58E-03
P00742	Coagulation factor X	↑	7.82	5.44E-03
Q99795	Cell surface A33 antigen	↑	8.14	5.63E-03
Q14353	Guanidinoacetate N-methyltransferase	↑	8.23	5.25E-03
P00492	Hypoxanthine-guanine phosphoribosyltransferase	↑	8.28	4.73E-03
P09525	Annexin A4	↑	8.55	4.63E-03
B0YIW2	Apolipoprotein C-III	↑	8.60	9.29E-03
Q6P4A8	Phospholipase B-like 1	↑	8.89	7.76E-03
P29373	Cellular retinoic acid-binding protein 2	↑	10.22	4.12E-03
Q96BW5	Phosphotriesterase-related protein	↑	10.85	2.76E-03
A0A096LPE2	SAA2-SAA4 readthrough	↑	10.97	3.60E-03
Q15149	Plectin	↑	11.07	2.35E-03
P51149	Ras-related protein Rab-7a	↑	12.62	5.25E-03
Q9BXJ7	Protein amnionless [Cleaved into: Soluble protein amnionless]	↑	13.84	1.06E-03
Q09328	Alpha-1,6-mannosylglycoprotein 6-beta-N-acetylglucosaminyltransferase A	↑	14.27	7.63E-03
Q9Y490	Talin-1	↑	14.73	8.81E-03
P16562	Cysteine-rich secretory protein 2	↑	15.01	6.75E-03
H0Y4H3	CD99 antigen-like protein 2	↑	16.01	9.45E-03
A5D8V6	Vacuolar protein sorting-associated protein 37C	↑	16.07	6.63E-03
Q9Y6X5	Bis(5'-adenosyl)-triphosphatase ENPP4	↑	16.22	8.25E-03
E7END7	Ras-related protein Rab-1A	↑	20.71	2.39E-03
Q9H190	Syntenin-2	↑	21.59	9.22E-03
H7BY57	Neurofascin	↑	22.82	4.66E-05
K7EIK7	EMAP like 2	↑	24.28	2.87E-03

表 S7 宽松条件下双相组与抑郁组相比产生的差异蛋白富集到的生物学过程和信号通路(P<0.05)

BP	P-Value	pathway	P-Value
cell adhesion	4.70E-13	Complement and coagulation cascades	2.70E-11
complement activation, classical pathway	1.20E-12	Regulation of actin cytoskeleton	1.40E-09
homophilic cell adhesion via plasma membrane adhesion molecules	9.30E-10	Necroptosis	1.00E-06
proteolysis	5.80E-09	Systemic lupus erythematosus	9.80E-06
innate immune response	7.40E-09	Proteoglycans in cancer	4.20E-05
cell-cell adhesion	4.00E-08	Shigellosis	1.70E-04
phagocytosis, recognition	4.50E-08	Endocytosis	2.20E-04
phagocytosis, engulfment	5.40E-08	Adherens junction	9.00E-04
positive regulation of B cell activation	2.70E-07	Amoebiasis	1.80E-03
positive regulation of canonical Wnt signaling pathway	3.70E-07	ECM-receptor interaction	2.50E-03
defense response to bacterium	5.50E-07	Focal adhesion	2.70E-03
adaptive immune response	1.20E-06	PI3K-Akt signaling pathway	3.00E-03
heterochromatin assembly	1.80E-06	Bacterial invasion of epithelial cells	3.60E-03
immunoglobulin mediated immune response	2.20E-06	Neutrophil extracellular trap formation	4.10E-03
B cell receptor signaling pathway	2.60E-06	Leukocyte transendothelial migration	4.20E-03
zymogen activation	3.30E-06	Cell adhesion molecules	5.50E-03
viral budding via host ESCRT complex	1.60E-05	Alcoholism	8.90E-03
immune response	1.80E-05	Rap1 signaling pathway	9.20E-03
non-canonical Wnt signaling pathway	2.10E-05	Tight junction	9.70E-03
adherens junction organization	2.20E-05	Biosynthesis of amino acids	1.10E-02
axon guidance	3.80E-05	Thiamine metabolism	1.20E-02
peptidyl-tyrosine phosphorylation	7.90E-05	Carbon metabolism	1.30E-02
blood coagulation	1.20E-04	Protein digestion and absorption	2.00E-02
multivesicular body assembly	1.30E-04	Pathogenic Escherichia coli infection	2.90E-02
blood coagulation, intrinsic pathway	1.30E-04	Tyrosine metabolism	2.90E-02
angiogenesis	1.30E-04	Mitophagy - animal	3.00E-02
signal transduction	3.20E-04	Staphylococcus aureus infection	3.80E-02
viral entry into host cell	3.20E-04	-	-
regulation of actin filament polymerization	4.70E-04	-	-
complement activation	4.80E-04	-	-
endocytosis	5.40E-04	-	-
synapse assembly	6.00E-04	-	-
cellular oxidant detoxification	6.50E-04	-	-
cell morphogenesis	7.50E-04	-	-
nucleobase-containing small molecule interconversion	8.80E-04	-	-
modification-dependent protein catabolic process	8.80E-04	-	-
ubiquitin-dependent protein catabolic process via the multivesicular body sorting pathway	1.10E-03	-	-
cell-cell junction assembly	1.20E-03	-	-

fibrinolysis	1.30E-03	-	-
calcium-dependent cell-cell adhesion via plasma membrane cell adhesion molecules	1.40E-03	-	-
ATP metabolic process	1.50E-03	-	-
antibacterial humoral response	1.60E-03	-	-
renal protein absorption	2.00E-03	-	-
immunoglobulin production	2.20E-03	-	-
negative regulation of cell death	2.20E-03	-	-
positive regulation of ERK1 and ERK2 cascade	2.30E-03	-	-
positive regulation of apoptotic process	2.40E-03	-	-
positive regulation of peptidyl-tyrosine phosphorylation	2.50E-03	-	-
regulation of peptidyl-tyrosine phosphorylation	2.70E-03	-	-
cell-cell adhesion via plasma-membrane adhesion molecules	2.90E-03	-	-
defense response to Gram-negative bacterium	3.10E-03	-	-
response to mechanical stimulus	3.50E-03	-	-
membrane fission	3.60E-03	-	-
Arp2/3 complex-mediated actin nucleation	3.70E-03	-	-
positive regulation of MAP kinase activity	3.80E-03	-	-
negative regulation of fibrinolysis	4.10E-03	-	-
receptor-mediated endocytosis	4.10E-03	-	-
response to lipopolysaccharide	4.20E-03	-	-
multicellular organism development	4.40E-03	-	-
plasma membrane repair	4.90E-03	-	-
response to cold	4.90E-03	-	-
canonical Wnt signaling pathway	5.10E-03	-	-
ossification	5.40E-03	-	-
cell-cell adhesion mediated by cadherin	5.60E-03	-	-
protein autoprocessing	5.60E-03	-	-
cell migration	5.70E-03	-	-
membrane to membrane docking	6.40E-03	-	-
regulation of organelle assembly	6.40E-03	-	-
positive regulation of tumor necrosis factor production	6.40E-03	-	-
defense response to Gram-positive bacterium	6.90E-03	-	-
protein homotrimerization	7.60E-03	-	-
maintenance of gastrointestinal epithelium	7.60E-03	-	-
positive regulation of T cell proliferation	7.80E-03	-	-
excretion	8.10E-03	-	-
platelet aggregation	8.60E-03	-	-
transmembrane receptor protein tyrosine kinase signaling pathway	8.70E-03	-	-
macroautophagy	9.00E-03	-	-

leukocyte cell-cell adhesion	9.10E-03	-	-
negative regulation of cell migration	9.10E-03	-	-
response to peptide hormone	9.40E-03	-	-
extracellular matrix organization	9.50E-03	-	-
animal organ morphogenesis	1.00E-02	-	-
positive regulation of kinase activity	1.00E-02	-	-
negative regulation of cell-substrate adhesion	1.10E-02	-	-
cell surface receptor signaling pathway	1.10E-02	-	-
positive regulation of neutrophil extravasation	1.30E-02	-	-
negative regulation of macrophage chemotaxis	1.30E-02	-	-
response to bacterium	1.30E-02	-	-
response to starvation	1.50E-02	-	-
actin filament bundle assembly	1.50E-02	-	-
triglyceride metabolic process	1.50E-02	-	-
positive regulation of I-kappaB kinase/NF-kappaB signaling	1.50E-02	-	-
negative regulation of peptidase activity	1.60E-02	-	-
response to glucocorticoid	1.60E-02	-	-
carbohydrate metabolic process	1.60E-02	-	-
actin polymerization or depolymerization	1.60E-02	-	-
establishment of endothelial barrier	1.60E-02	-	-
myoblast differentiation	1.60E-02	-	-
regulation of centrosome duplication	1.60E-02	-	-
glycosaminoglycan catabolic process	1.60E-02	-	-
positive regulation of interferon-gamma production	1.70E-02	-	-
lung-associated mesenchyme development	1.70E-02	-	-
fibroblast growth factor receptor signaling pathway	1.70E-02	-	-
acute-phase response	1.80E-02	-	-
protein transport	1.80E-02	-	-
T cell costimulation	2.00E-02	-	-
actin filament polymerization	2.00E-02	-	-
cellular iron ion homeostasis	2.10E-02	-	-
regulation of synapse organization	2.10E-02	-	-
barbed-end actin filament capping	2.10E-02	-	-
positive regulation of Wnt signaling pathway	2.10E-02	-	-
positive regulation of early endosome to late endosome transport	2.10E-02	-	-
cyclooxygenase pathway	2.10E-02	-	-
negative regulation of complement activation, classical pathway	2.10E-02	-	-
protein folding	2.20E-02	-	-
epidermis development	2.30E-02	-	-

positive regulation of cell proliferation	2.60E-02	-	-
protein localization to plasma membrane	2.60E-02	-	-
multicellular organismal iron ion homeostasis	2.60E-02	-	-
cellular response to platelet-derived growth factor stimulus	2.60E-02	-	-
response to food	2.60E-02	-	-
positive regulation of establishment of protein localization to telomere	2.60E-02	-	-
branching involved in salivary gland morphogenesis	2.60E-02	-	-
morphogenesis of an epithelial sheet	2.60E-02	-	-
nucleoside monophosphate phosphorylation	2.60E-02	-	-
positive regulation of protein localization to early endosome	2.60E-02	-	-
interleukin-1-mediated signaling pathway	2.90E-02	-	-
negative regulation of cell proliferation	3.00E-02	-	-
multivesicular body-lysosome fusion	3.20E-02	-	-
vesicle fusion with vacuole	3.20E-02	-	-
positive regulation of protein localization to Cajal body	3.20E-02	-	-
hydrogen peroxide catabolic process	3.20E-02	-	-
response to xenobiotic stimulus	3.30E-02	-	-
negative regulation of interleukin-2 production	3.50E-02	-	-
leukocyte migration	3.50E-02	-	-
cellular response to retinoic acid	3.50E-02	-	-
protein stabilization	3.50E-02	-	-
intracellular transport	3.60E-02	-	-
wound healing	3.60E-02	-	-
regulation of blood coagulation	3.70E-02	-	-
regulation of complement activation	3.70E-02	-	-
regulation of cell-cell adhesion	3.70E-02	-	-
cell surface pattern recognition receptor signaling pathway	3.70E-02	-	-
negative regulation of cytokine-mediated signaling pathway	3.70E-02	-	-
response to electrical stimulus	3.90E-02	-	-
nucleus organization	3.90E-02	-	-
cellular response to reactive oxygen species	4.00E-02	-	-
positive regulation of cell migration	4.10E-02	-	-
receptor internalization	4.30E-02	-	-
epidermal growth factor receptor signaling pathway	4.30E-02	-	-
ephrin receptor signaling pathway	4.30E-02	-	-
cellular response to interleukin-7	4.30E-02	-	-

actin filament severing	4.30E-02	-	-
positive regulation of integrin-mediated signaling pathway	4.30E-02	-	-
actin nucleation	4.30E-02	-	-
regulation of gene expression	4.50E-02	-	-
cellular response to mechanical stimulus	4.80E-02	-	-
negative regulation of angiogenesis	4.80E-02	-	-
osteoblast differentiation	4.80E-02	-	-
epithelial cell differentiation	4.80E-02	-	-
negative regulation of Wnt signaling pathway	4.80E-02	-	-
autophagy	4.90E-02	-	-

表 S8 抑郁组单例样本与健康组相比 12 例及以上样本共有的差异蛋白

差异蛋白编号	差异蛋白名称	差异蛋白变化趋势
Q96IQ7	V-set and immunoglobulin domain-containing protein 2	13↑
P0DOX5	Immunoglobulin gamma-1 heavy chain	13↓
A0A075B6S2	Immunoglobulin kappa variable 2D-29	13↓
P01833	Polymeric immunoglobulin receptor	13↓
O00187	Mannan-binding lectin serine protease 2	13↓
P50591	Tumor necrosis factor ligand superfamily member 10	13↓
P01859	Immunoglobulin heavy constant gamma 2	13↓
P01834	Immunoglobulin kappa constant	13↓
P10153	Non-secretory ribonuclease	13↓
P10451	Osteopontin	13↓
C9IZ46	Protein shisa-5	13↓
O75339	Cartilage intermediate layer protein 1	13↓
Q96FE7	Phosphoinositide-3-kinase-interacting protein 1	13↓
P07998	Ribonuclease pancreatic	13↓
P01009	Alpha-1-antitrypsin	13↓
P01042	Kininogen-1	13↓
P10253	Lysosomal alpha-glucosidase	2↑11↓
P15328	Folate receptor alpha	2↑11↓
P00734	Prothrombin	2↑11↓
Q8WZ75	Roundabout homolog 4	2↑11↓
B8ZZQ6	Prothymosin alpha	2↑11↓
A0A087X0K0	Collagen type XV alpha 1 chain	2↑11↓
P02790	Hemopexin	2↑11↓
P02790	Hemopexin	2↑11↓
A0A2R8Y478	CD9 molecule	7↑6↓
Q13740	CD166 antigen	12↑
Q86SF2	N-acetylgalactosaminyltransferase 7	12↑
Q9Y5F6	Protocadherin gamma-C5	12↑
I3L4I4	Target of myb1 like 1 membrane trafficking protein	12↑
Q8IWU5	Extracellular sulfatase Sulf-2	12↓

P0DP57	Secreted Ly-6/uPAR domain-containing protein 2	12↓
Q6EMK4	Vasorin	12↓
P07602	Prosaposin	12↓
A0A0G2JLV7	Leukocyte-associated immunoglobulin-like receptor 1	12↓
Q16651	Prostasin	12↓
P02760	Protein AMBP	12↓
P12109	Collagen alpha-1(VI) chain	12↓
O75594	Peptidoglycan recognition protein 1	12↓
P05090	Apolipoprotein D	12↓
G3V4U0	Fibulin 5	12↓
P01876	Immunoglobulin heavy constant alpha 1	12↓
J3QQX6	Intercellular adhesion molecule 2	12↓
D6RBV2	Lectin, mannose binding 2	12↓
P02768	Albumin	12↓
O60494	Cubilin	1↑11↓
Q6UXB8	Peptidase inhibitor 16	1↑11↓
P01034	Cystatin-C	1↑11↓
P60022	Beta-defensin 1	1↑11↓
Q9NZP8	Complement C1r subcomponent-like protein	1↑11↓
P61970	Nuclear transport factor 2	1↑11↓
P0DOX8	Immunoglobulin lambda-1 light chain	1↑11↓
P61769	Beta-2-microglobulin	1↑11↓
P05060	Secretogranin-1	1↑11↓
P04745	Alpha-amylase 1A	1↑11↓
A0M8Q6	Immunoglobulin lambda constant 7	1↑11↓
Q9HCU0	Endosialin	2↑10↓
P01624	Immunoglobulin kappa variable 3-15	2↑10↓
P08294	Extracellular superoxide dismutase [Cu-Zn]	3↑9↓
Q7LBR1	Charged multivesicular body protein 1b	3↑9↓
Q9NPF0	CD320 antigen	3↑9↓
Q13201	Multimerin-1	4↑8↓
O00560	Syntenin-1	4↑8↓
Q99784	Neuronal olfactomedin-related ER localized protein	8↑4↓
P11717	Cation-independent mannose-6-phosphate receptor	5↑7↓
A0A0C4DH35	Probable non-functional immunoglobulin heavy variable 3-35	7↑5↓
Q7Z7M0	Multiple epidermal growth factor-like domains protein 8	6↑6↓